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REVIEW

Poly(ADP-Ribose) Polymerases in Host-Pathogen Interactions, Inflammation, and Immunity

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SUMMARY The literature review presented here details recent research involving members of the poly(ADP-ribose) polymerase (PARP) family of proteins. Among the 17 recognized members of the family, the human enzyme PARP1 is the most extensively studied, resulting in a number of known biological and metabolic roles. This review is focused on the roles played by PARP enzymes in host-pathogen interactions and in diseases with an associated inflammatory response. In mammalian cells, several PARPs have specific roles in the antiviral response; this is perhaps best illustrated by PARP13, also termed the zinc finger antiviral protein (ZAP). Plant stress responses and immunity are also regulated by poly(ADP-ribosyl)ation. PARPs promote inflammatory responses by stimulating proinflammatory signal transduction pathways that lead to the expression of cytokines and cell adhesion molecules. Hence, PARP inhibitors show promise in the treatment of inflammatory disorders and conditions with an inflammatory component, such as diabetes, arthritis, and stroke. These functions are correlated with the biophysical characteristics of PARP family enzymes. This work is important in providing a comprehensive understanding of the molecu-

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lar basis of pathogenesis and host responses, as well as in the identification of inhibitors. This is important because the identification of inhibitors has been shown to be effective in arresting the progression of disease.

KEYWORDS ADP-ribosylation, poly(ADP-ribose) polymerases, poly(ADP-ribose), antiviral responses, autoimmunity, enzyme inhibition, host-pathogen interactions, inflammation, stress granules, transcriptional regulation

INTRODUCTION

Poly(ADP-ribose) (PAR) is an unusual nucleic acid that is derived from NAD^+ by the action of poly(ADP-ribose) polymerase (PARP) enzymes. This polymer is usually found as a posttranslational modification of proteins and performs a wide variety of signaling, regulatory, and metabolic functions in cells. Essential functions in DNA damage repair, RNA biology, stress responses, the cell cycle and cell death pathways, gene expression regulation, chromatin remodeling, and others have been identified (1). PAR was originally identified in 1963 by the laboratories of P. Chambon and coworkers as the insoluble portion of hen liver nuclear extracts (2). Subsequently its primary structure was determined by the Mandel, Hayaishi, and Kawamura laboratories independently (3–5). Enzymes responsible for poly(ADP-ribose) polymerase and mono(ADP-ribosyl)transferase (MART) activities were subsequently discovered in the 1980s and 1990s, respectively (6–9). A distinction is now made between PARPs, which catalyze ADP-ribose (ADPR) polymerization or poly(ADP-ribosyl)ation, and enzymes that transfer a single ADP-ribose monomer. The latter is termed mono(ADP-ribosyl)ation (MARylation). The entire enzyme family is now also referred to as diphtheria toxin-like ADP-ribosyltransferases (ARTDs), referring to their mechanistic similarity to the ADP-ribosylating diphtheria toxin proteins (10).

Seventeen human PARP enzymes have been identified (10). In addition, approximately 1,900 other PARP family enzymes have been identified in other organisms, primarily eukaryotes (11–13). Table 1 lists the most current nomenclature of PARPs/ARTDs along with other names associated with PARP protein family members.

PARP family members have essential roles in the cell. Well-characterized roles exist, for example, in DNA damage repair. PARP1 and PARP2 are important components of the single-strand break (SSB) repair and base excision repair pathways. PARP1 and PARP3 participate in double-strand break (DSB) repair (reviewed in reference 14). Other roles include regulating the cell cycle, regulating transcription, participating in chromatin remodeling, and interacting with epigenetic mechanisms (15–18). When acting as transcriptional cofactors, PARPs participate in regulating circadian rhythms, guiding embryonic development, reprogramming somatic cells, and cellular differentiation (19–27). Additional roles in RNA biochemistry have recently been discovered. PARPs participate in the regulation of ribosome biogenesis and nucleolar structure and assist in controlling mRNA stability and translation (22, 28–34). PARP activity also impacts the regulation of alternative splicing and RNA silencing (35–37).

PARPs play significant roles in the development of cancer and have been shown to contribute to six of the eight "hallmarks of cancer": metastasis, replicative immortality, angiogenesis, cell death resistance, avoidance of growth suppression, proliferative signaling, deregulation of cellular energetics, and avoidance of immune destruction (38). Through these functions, PARP inhibition has become important in treating several types of cancer, and several PARP inhibitors have been successful in clinical trials. Examples include the compounds olaparib and veliparib, which are applied to the treatment of ovarian, breast, and lung cancers (39).

This review discusses emerging roles of PARPs and poly(ADP-ribosyl)ation (PARylation) in inflammation, immunity, and host-pathogen interactions. Increasing evidence shows that PARPs have importance in viral infection, often being coopted by both DNA and RNA viruses. PARPs also contribute to inflammatory responses, and PARP inhibition shows promise for the treatment of chronic inflammatory conditions. Recent studies

TABLE 1 Nomenclature, predicted mode of PARylation, and novel biological roles in immune response to pathogens and inflammatory response of PARP family enzymes[a]

PARP name	ARTD name	Alternative name	Catalysis mode	Novel biological role(s) in inflammatory and autoimmune diseases
PARP1	ARTD1		Poly	Antiviral and proviral functions; anti- and proinflammatory responses
PARP2	ARTD2		Poly	Pathogen response
PARP3	ARTD3		Poly	
PARP4	ARTD4	vPARP	Poly	Antiviral
PARP5a	ARTD5	Tankyrase 1	Poly	Antiviral
PARP5b	ARTD6	Tankyrase 2	Poly	Proinflammatory
PARP6	ARTD17		Mono	
PARP7	ARTD14	TI PARP	Mono	Antiviral
PARP8	ARTD16		Mono	
PARP9	ARTD9	BAL1	Mono	Antiviral
PARP10	ARTD10		Mono	Antiviral and anti-inflammatory
PARP11	ARTD11		Mono	
PARP12	ARTD12		Mono	Antiviral
PARP13	ARTD13	ZAP1	Inactive	Antiviral
PARP14	ARTD8	BAL2	Mono	Antiviral and anti-inflammatory
PARP15	ARTD7	BAL3	Mono	Antiviral
PARP16	ARTD15		Mono	Proinflammatory

[a]List of the most current nomenclature of the PARP family of proteins (both formal and common), the classifications of the enzymes with respect to their mono(ADP)ribosylation (Mono) or poly(ADP)ribosylation (Poly) catalytic activity, and novel biological roles of the proteins in immune and inflammatory responses. Several PARP enzymes (PARP3, -6, -8, and -11) have yet to have roles in either the immune or inflammatory responses identified (10, 624, 636).

also show that PARPs participate in responses to infection, and other stress responses, in various organisms.

FUNCTION AND CLASSIFICATION OF PARP ENZYMES

Classification of PARP enzymes is based on the reactions catalyzed combined with phylogenetic analysis and domain structure. As illustrated in Fig. 1, each protein has a unique domain structure, though similarities are present. For example, the C-terminal PARP catalytic (CAT) domain, which is the site at which ADP-ribosyl transfer occurs (40), is found in PARP enzymes and contains an ART fold that is conserved throughout the PARP family as well as a helical domain (HD) that is conserved in the DNA damage response PARPs (41, 42). In PARP4, an enzyme localized to cytoplasmic vaults, the catalytic domain is located at the N terminus. The catalytic triad often indicates the function of the protein and is one way in which the enzymes can be categorized. In PARP1, the catalytic domain is characterized by a 50-amino-acid signature sequence which is conserved in vertebrates and also displays partial conservation among all species (43).

Of the known human PARPs, five (PARP1, PARP2, PARP4, PARP5a, and PARP5b) are polymerases in that they form polymers. These five PARPs share a conserved catalytic triad consisting of histidine, tyrosine, and glutamate (H-Y-E) residues. Ten were shown to transfer a single ADP-ribose unit and are classified as mono(ADP-ribosyl)transferases (MARTs), namely PARP3, PARP6 to -12, and PARP14 to -16 (44–46). PARP6, -8, and -16 are grouped together based on phylogenetic analysis of PARP catalytic domains (12). One human PARP protein, PARP13, is so far believed to be catalytically inactive (44). Table 1 lists the transferase activity of each enzyme.

The presence of a variety of other domains appears to generate many other biological and biochemical functions for this family of proteins and allows them to be grouped into subfamilies on the basis of their functions (47). In 2006, Schreiber et al. proposed classifying PARPs into the following groups on the basis of their identified functional domains and presumed functions: (i) DNA-dependent PARPs, which act as molecular sensors of DNA breaks and play a role in the spatial and temporal aspects of DNA repair; (ii) tankyrases, which play a role in telomere homeostasis; (iii) CCCH-type PARPs, which contain zinc fingers and whose sites of expression indicate a possible role in neurological functions; and (iv) macro-PARPs, which consist of conserved macrodo-

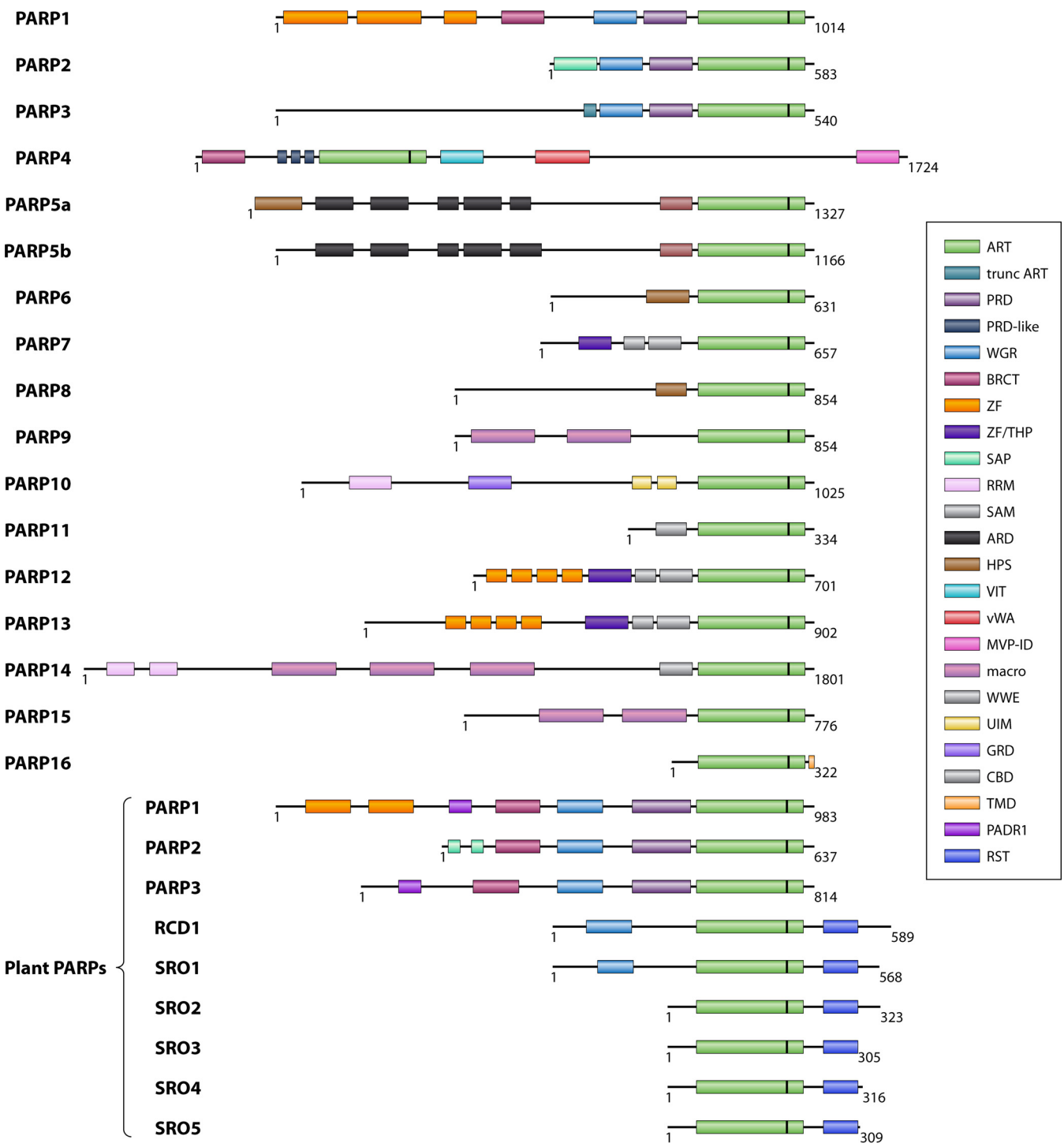

FIG 1 Domain structure of the human PARP family of enzymes, showing the variation in the length of the sequence and domain structure. The ART is the catalytic domain of the sequences, some of which have a conserved sequence comprised of residues 859 to 908. In addition, in select PARPs, a catalytic glutamic acid corresponding to position 988 of PARP1 has been identified and is highlighted by a shaded region in the ART domain. The helical domain (HD) is the PARP regulatory domain which is involved in the activation of the enzyme and regulation of the branching of PAR structures. WGR is a domain in which the characteristic sequence Trp-Gly-Arg is present. The BRCT domain is the BRCA1 carboxyl-terminal domain which is found in many cell cycle and DNA damage repair proteins. Within the BRCT domain lies the automodification domain (AMD), which is responsible for some of the dimerization of PARP enzymes. ZF is the zinc finger domain, which participate in DNA binding, and ZF/THP is the TiPARP homologous domain. SAP is the SAF/Acinus/PIAS-DNA-binding domain. RRM is the RNA-binding/recognition motif. SAM is the sterile alpha motif, which is often found in signaling and nuclear proteins. ARD is the Ankyrin repeat domain, which helps to mediate protein-protein interactions between proteins from diverse families. The HPS domain is the His-Pro-Ser region. Both the VIT (vault protein interalpha-trypsin) and the vWA (von Willebrand type A) domains are conserved regions that are both thought to mediate protein-protein interactions. MVP-ID is the major-vault particle interaction domain. Macrodomain, poly(ADP-ribose) interaction domain; WWE, iso(ADP-ribose) and protein-protein interaction domain with Trp-Trp-Glu conserved sequence. UIM is the MAO interaction motif, GRD is a glycine-rich domain. And TMD is the transmembrane domain. CCCH is the Cys-Cys-Cys-His zinc finger domain (10, 181, 637).

mains that are linked to a PARP domain. There are several PARP family members that are not classed among these groups, i.e., PARP4, PARP6, PARP8, PARP10, and PARP11 (47).

PARPs in DNA Repair

Though PARPs perform numerous functions, there are several broad categories that are well established. The first is as a DNA damage response protein. PARP1, PARP2, and PARP3 are DNA-dependent enzymes that are activated upon binding to DNA damage and play important roles in the repair of DNA strand breaks (48). To date, three PARP enzymes (PARP1, -2, and -3) have been identified to play a role in DNA repair, with the role of PARP1 having been studied the most extensively (49–51). PARP1 has been proposed as a general DNA damage sensor and is activated by several types of damaged DNA, including hairpins, cruciform DNA, loops, nicked DNA, blunt ends, and overhangs (52, 53). PARP1 may also interact with other non-B DNA structures, such as G quadruplexes (54). In contrast, PARP2 and -3 play more specific roles in DNA repair pathways. PARP2 participates in the base excision repair (BER) pathway, interacting with the X-ray repair cross-complementing protein 1 (XRCC1) and DNA ligase III (55, 56). The depletion of PARP2 results in an increased sensitivity to ionizing radiation and alkylating agents, which is consistent with a role in single-strand break (SSB) repair (55, 57). PARP2 is the closest paralogue of PARP1 and in the presence of DNA damage is responsible for most of the residual PARP activity in PARP1$^{-/-}$ cells (50, 58). While either PARP1 or PARP2 can be knocked out in mice without causing serious defects, a double knockout is lethal in the embryo, suggesting that the functions of these two enzymes are partly redundant (57).

In contrast, PARP3 has been shown to play a role in double-strand break (DSB) repair by interacting with the aprataxin-like factor (APLF) at damaged sites (49, 59). PARP3 also helps to promote accurate ligation of DSB by XRCC4 and DNA ligase IV during the nonhomologous end-joining (NHEJ) process (49, 60). PARP3 was shown to ADP-ribosylate histone H2B, and this was required for the SSB response (61). PARP2 and PARP3 enzymes are activated by a smaller subset of damaged DNA types, which is consistent with their specific roles. Thus, PARP2 is activated by DNA containing "flaps and gaps" (62), while PARP3 is activated by blunt ends (49). Both enzymes are activated by 5′-phosphorylated nicks (42).

PARP1 to -3 also have the capacity to ADP-ribosylate DNA, with the modification occurring at double-strand break termini. This activity may help to mark the locations of strand breaks and recruit repair proteins (63–65).

PARP as a Chromatin-Remodeling Protein

A second category of biological function for PARPs is their role in chromatin remodeling. MARylation and PARylation of histones were observed as early as 1980 (66, 67). PARP was soon observed to participate in the relaxation or decondensation of chromatin structure (68–71). The addition of a high-molecular-weight, negatively charged polymer to histone proteins loosens the tightly packed structure of chromatin by electrostatic repulsion, promoting the access of chromatin-remodeling factors (68). PARP was shown to participate in puffing in *Drosophila,* a process which requires the loosening of chromatin structure, promoting remodeling and facilitating transcription (72). Not only PARylation but also MARylation has unique roles; for example, MARylation of histone H3 promotes the access of p300, leading to cellular proliferation through the β-catenin pathway (73). Changes in nucleosome structure due to PARP binding and PARylation were shown to lead to high gene transcription levels and could produce, for example, a strong inflammatory response due to recruitment of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) at the interleukin-1β (IL-1β) and tumor necrosis factor (TNF) promoters where PARP1 is constitutively associated (74). The nucleosome-binding capability of PARP1 was shown to be key to its transcription factor coactivator activity for certain loci (75) (see also "PARPs as Transcription Factor Coactivators/Corepressors" below).

PARP1 also participates in the recruitment of other proteins which modify chromatin. Imitation switch (ISWI) is a target of covalent PARylation (76); PARylation downregulates ISWI function. Covalent PARylation of chromatin-remodeling proteins functions to regulate their activity (76). One of the best-studied examples is chromodomain-helicase-DNA-binding protein 1-like (CHD1L), also called amplified in liver cancer protein 1 (ALC1). This protein functions to promote the relaxation of chromatin at sites of DNA damage, a mechanism that is dependent on the formation of a stable PAR-mediated intermediate formed by ALC1 and PARP1 (77). PARP1 activation mediates ALC1 activation through an allosteric mechanism (78, 79). This activity is important for single-strand break repair (80–82). Direct remodeling of nucleosomes by PARylation was recently observed to facilitate transcription factor recruitment and gene transcription (83).

Under certain conditions, PARP1 can also promote chromatin compaction and transcriptional repression, through binding of specific domains to nucleosomes (84). PARP1 can function both as a chromatin architectural protein and as a nucleosome assembly factor, depending on whether the enzyme itself is automodified with PAR chains. In the absence of NAD^+, PARP is able to bind nucleosomes and condense chromatin (85). Upon automodification and enzyme activation, the affinity of PARP for nucleosomes is decreased and the chromatin structure is relaxed. In addition to histone PARylation, PARP participates in histone chaperone and nucleosome assembly processes (86).

PARPs as Transcription Factor Coactivators/Corepressors

A third category of biological function is for PARPs that act as transcription factors or transcription factor-binding partners, where they serve as coactivators or corepressors (87–95). For example, PARP1 regulates the function of several ubiquitous eukaryotic transcription factors such as specificity protein 1 (SP1), Ets-1, p53, and nuclear factor of activated T cells (NFAT) (87–95). PARP1 inhibits the negative elongation factor (NELF) to enhance effective transcription by RNA polymerase II (96). PARP6 assists in the negative regulation of cell cycle progression as a function of the activity of its catalytic domain (97). PARP7 participates in the negative feedback regulation of the arylhydrocarbon receptor (AHR) signaling pathway (98). Additionally, PARP7 has been shown to structurally modify and coactivate liver X receptors α and β, which are important regulators in lipid and glucose metabolism, as well as inflammatory pathways. This has established the protein's function as a regulator of nuclear transcription factors (98, 99). Similarly, PARP10 and PARP14 both function as regulators of gene transcription (100–103). PARP9 and PARP10 both modulate transcription and participate in the DNA damage response (103–105). A role for PARP1 in cotranscriptional gene splicing has been identified (33).

PARPs also interact with other players in epigenetic processes. Histone acetyltransferases (HATs) and PARPs were observed to cooperate in regulating transcription (106). For example, upon PARP inhibition, a global decrease in histone acetylation was observed. This was found to be due to an increase in histone deacetylase (HDAC) activity. Further, PARP1 positively regulates the transcription of the HATs p300, CREB-binding protein (CBP), and PCAF; p300 and CBP are also PARylation substrates (107, 108). In addition, PARylation has been observed to correlate with the downregulation of acetylation levels (109).

An interaction between PARylated PARP in chromatin and HDACs is believed to be required to maintain HDAC activity and thus a balanced H3 acetylation level. This correlates with physical interactions with HDACs that were previously observed (110). Similarly, PARP14 has also been described as a transcriptional coactivator/corepressor that partners with HDACs to facilitate Stat6-dependent transcription in response to IL-4 (102). In addition, PARP1 interacts with and regulates DNA methyltransferase 1 (111) through PARylation of the histone demethylase lysine-specific demethylase 5B (KDM5B) (112). This interaction can regulate the expression of specific genes, for example, preventing the methylation of CCCTC-binding factor (CTCF) promoter sites (16).

New functions within and outside these categories continue to be discovered. Recent proteomic work has identified ADP-ribosylation substrates, which is useful for understanding the metabolic pathways involving PARPs (113–117). The results of these studies suggest that PARPs regulate many more biological functions than have been identified to date (113). Among the novel functions identified for this family of enzymes are their roles in host-pathogen interactions. Some of the most recent findings are discussed below.

PARPs IN HOST-PATHOGEN INTERACTIONS

PARPs in Antiviral Responses

A major advance in the involvement of PARPs in antiviral responses was the identification of PARP13, also known as the zinc finger antiviral protein or ZAP1, as an antiviral factor. PARP13 targets both RNA and DNA viruses, including influenza virus, alphavirus, filovirus, herpesvirus, and HIV (118–123). Its mechanisms of action include the induction of interferon (IFN) signaling through interaction with retinoic acid-inducible gene I (RIG-I) and other interferon-stimulated genes (ISGs) (123–126). PARP13 also interacts with the Moloney leukemia virus 10 homologue (MOV10) RNA-induced silencing complex RNA helicase, inhibiting retrotransposition and retroviruses. Another mechanism involves the physical interaction of PARP13 with argonaute proteins to target them for ADP-ribosylation (127), thus activating antiviral genes that are silenced via the RNA interference (RNAi) machinery under normal conditions (119). PARP13 recruits the exosome and the deadenylase poly(A)-specific RNase (PARN), as well as the 5′-3′ degradation machinery to degrade viral RNAs (121). Figure 2 summarizes several currently known antiviral functions of PARPs.

Further studies showed that PARP13's roles in the cell are not limited to participating in the antiviral response. The protein targets both viral and host transcripts, resulting in the induction of apoptotic pathways (degradation) and inhibiting viral replication (121, 123, 126). PARP13 is therefore considered to have specific roles in cellular mRNA decay (128).

An orthologous protein that shares sequence similarity with PARP13 but is catalytically active is PARP12. PARP12 shares some of the observed roles of PARP13 in RNA decay and in the antiviral response. Like PARP13, it recognizes specific sequences in viral RNA and DNA and degrades retroviral RNA (121, 122, 125). Both proteins contain zinc finger domains in the N-terminal region. Recognition of RNA by these nucleic acid-binding domains is required for antiviral activity (129, 130). The structure of these domains has been solved and showed unusual, CCCH-type zinc fingers with cavities that could bind RNA in a looped conformation (130).

The RNA decay pathways mediated by PARP12 and -13 are an important mechanism of host cell defense but not the only mechanism involving PARPs. At least eight human PARPs have demonstrated antiviral activity (identified in Table 1). Another mechanism that has been demonstrated is the specific interaction of PARPs with viral proteins to promote proteasomal degradation. PARP1 associates with the herpesvirus RTA protein, which acts as a molecular switch to suppress lytic replication (131). PARP1 is correspondingly downregulated during lytic replication (131–134). PARP1 is additionally targeted for ubiquitination and proteasomal degradation by the viral processivity factors (PF-8) and open reading frame 59 (ORF59), which has the effect of promoting lytic replication (133).

PARP10, -12, -13, and -14 are all induced by interferons, and all can inhibit viral replication (135, 136). PARP7 and PARP10, which are MARTs, are capable of translation inhibition. These proteins form complexes with ribosomes that are mediated by their N-terminal RNA-binding domains (137). Translation inhibition prevents viral growth by stopping viral protein synthesis. The finding that the induction of PARP10, -12, -13, and -14 can result in the inhibition of virus replication is consistent with previous results supporting the importance of PARPs in the inhibition of viral replication (135, 136).

PARP12 is induced by RNA virus infection and also inhibits cellular translation. The long isoform of PARP12, containing the PARP catalytic domain, rather than the short

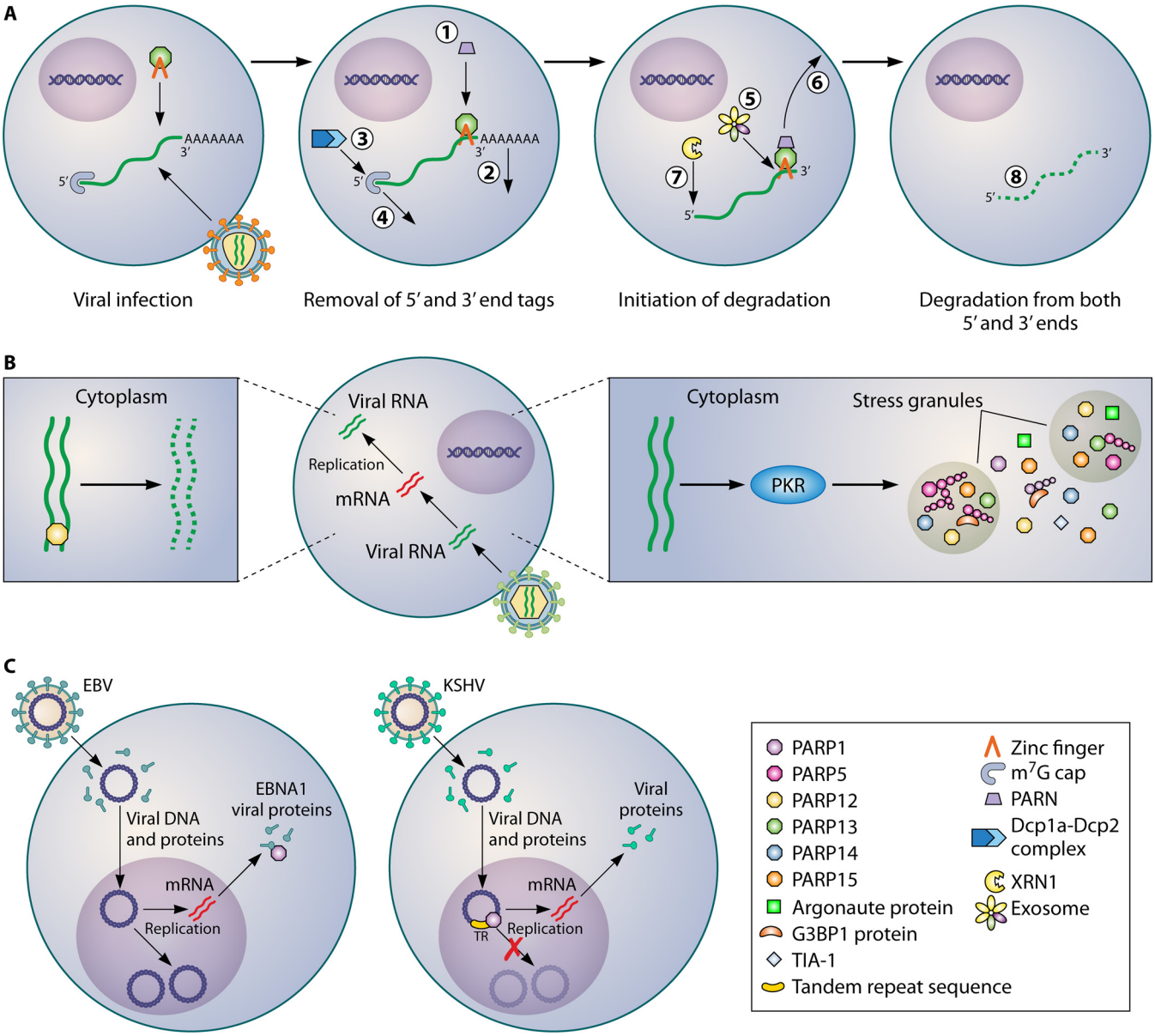

FIG 2 Roles of PARPs in the immune response after pathogen invasion. (A) Viral RNA degradation in a cell. Viral RNA is equipped with a m7G cap and a poly(A) tail at the 5′ and 3′ ends of the sequence, respectively. PARP13 has a role in this process though a binding interaction, which initiates a series of other actions. Upon binding though its N-terminal zinc finger region to the 3′ end of the viral RNA sequence (1), degradation factors are recruited. At the 3′ end, a deadenylase known as poly(A)-specific RNase (PARN) binds to PARP13, prompting the removal of the tail (2). At the 5′ end, a decapping complex formed by dcp1a and dcp2 (3) performs the removal of the m7G cap (4). A second degradation factor known as the exosome binds the zinc finger region of PARP13 through its RRP46 and RRP42 subunits (green and purple), signaling the 3′-5′ degradation process (5). In addition, PARP13 is removed from the RNA molecule (6). At the 5′ end a second exoribonuclease known as XRN1 initiates the degradation of the 5′ end of the sequence (7). This pathway results in the degradation of viral RNA from both the 5′ and 3′ ends of the sequence (8). (B) Some of the roles of other PARP family members following the infection of a host cell by a RNA virus. Following replication, PARP12 has also been shown to degrade viral RNA. In addition, the presence of viral RNA in the cytoplasm activates protein kinase RNA-activated ISGs which initiate the production of stress granules, where PARP5, -12, -13, -14, and -15 can be found. These PARPs function to modify other proteins such as the argonaute proteins, G3BP1, and TIA-1. In the cytoplasm, they also act to modify proteins by PARylation and are thought to function as scaffolds to recruit other RNA-binding proteins. (C) Immune responses following the infection of a host cell by two DNA viruses. PARP1 has been shown to posttranslationally modify Epstein-Barr nuclear antigen 1 (EBNA1) which modifies its dyad conformation. PARP1 binds to the terminal repeat sequence of Kaposi's sarcoma herpesvirus (KSHV), resulting in the inhibition of viral replication (133, 638, 639).

isoform was required for this antiviral activity, which was active against positive, negative, and ambisense RNA viruses (135). Since this mechanism appears to involve catalytic activity and/or the catalytic domain, it may be separate from the RNA decay functions of the protein.

Another important antiviral mechanism involves the formation of cellular stress granules (SGs). The introduction of viral RNA into the cytoplasm results in the activation

of protein kinase RNA (PKR)-activated SGs and the production of these membraneless organelles, which assist in arresting proviral cellular processes such as translational pathways. These organelles also regulate mRNA stability and have antiviral functions (reviewed in reference 138). Viruses use various strategies to disrupt or block stress granules; for example, Ebola virus inhibits SG formation (139), influenza virus sequesters double-stranded RNA (dsRNA) to prevent SG initiation (140), and poliovirus 3 C protease cleaves a major SG protein, Ras GTPase-activating protein-binding protein 1 (G3BP1) (141). The RNA-binding PARP12 and -13 are found in stress granules, where PARP12 is responsible for MARylation of various proteins such as the argonaute proteins, G3BP1, and TIA-1 (36). G3BP1 MARylation promotes stress granule nucleation (36). PARylation controls the sequestration of argonaute 2 (AGO2), leading to the modulation of microRNA silencing (36). PAR is able to nucleate phase transitions of RNA-binding proteins by initiating the liquid demixing process that is required for the formation of membraneless organelles (142, 143). PARP5a, -7, and -15 have also been localized to stress granules (36). Along with PARP12 and -13, PARP5a, -14, and -15 were suggested to have regulatory roles in the production and maintenance of stress granules (36). This is illustrated in Fig. 2B. Poly(ADP-ribose) glycosylase (PARG) also localized to SGs, and its overexpression inhibited SG formation, again suggesting a key role of PAR in SGs (36).

Several other PARPs have been identified to have antiviral functions. PARP14 has an active role in the development of T cells and B cells. This process is initiated by interleukin-4, which stimulates differentiation of Th2 cells, resulting in the ADP-ribosylation of HDACs. The deacetylation of chromatin allows the transcription of genes coding for immune cell production (102). PARP9 is a binding partner of Deltex 3-like, an E3 ubiquitin ligase that ubiquitinates histone H4 and protects cells against DNA damage. In the presence of its binding partner, PARP9 MARylates ubiquitin, preventing E3 ligase activity and providing regulation of the complex (46). The PARP9-Deltex 3-like complex also activates signal transducer and activator of transcription 1 (STAT1) and ubiquitinates histone proteins to promote the expression of a subset of interferon-stimulated genes, thereby stimulating the innate immune response. This complex also binds to viral 3C proteases and ubiquitinates them for degradation (144).

Phylogenetic analyses also support a role of PARP in antiviral defense. An analysis of PARP mutation rates showed positive selection in the catalytic domains of PARPs, suggesting a connection between the antiviral response and the activity of multiple PARPs, which is indicative of immune system defense (145, 146).

In the presence of DNA damage, PARP1 is responsible for the majority of cellular PARP activity (50, 58, 147, 148). Perhaps not surprisingly, this enzyme also performs antiviral functions. These occur through several mechanisms.

The release of viral contents into a cell initiates the host cell immune response, activating proapoptotic factors such as p53. Some viruses, such as Kaposi's sarcoma herpesvirus (KSHV), inhibit the action of p53, arresting apoptosis through a mechanism involving the ORF8 protein (149). PARP1 binds the terminal repeat (TR) sequence of KSHV, resulting in the inhibition of viral replication (Fig. 2C) (133).

Another mechanism takes advantage of PARP1's function as a chromatin-binding protein. PARP1 represses the expression of retrotransposons in *Drosophila* and of retroviruses in avian cells. This repression is mediated by HDACs and DNA methylases (150). Incorporation of PARP1 into chromatin causes chromatin compaction and transcriptional repression, which leads to retrotransposon silencing and the induction of heterochromatin. Upon activation of PARP1, the enzyme auto-PARylates and dissociates, leading to transcriptional activation and chromatin decompaction. Since other PARP family members also interact with HDACs (102), this may represent a common mechanism in the PARP family.

In a related manner, PARP1 has a role in HIV DNA integration. PARP1 is incorporated into nucleosomes in a manner that requires the N-terminal DNA-binding region and the interaction of the C-terminal region with histone proteins (151). PARP1 participates in HIV-1 long terminal repeat function, binds to HIV *trans*-activation response element

(TAR) RNA, and is required for efficient HIV-1 integration (152–154). Thus, by the same mechanism PARP1 can participate in a proviral or antiviral function, depending on the stage of the infectious cycle of the virus.

PARPs in Proviral Responses

In addition to performing antiviral functions, other cases are known in which PARPs are recruited by viruses to perform essential functions. For example, Epstein-Barr nuclear antigen 1 (EBNA1) of Epstein-Barr virus (EBV) is posttranslationally modified by PARP1, which leads to a remodeling of proteins at the dyad symmetry (DS) element (155) (Fig. 2C). PARP1 is believed to serve a dual role, both preventing DNA damage and regulating the efficiency of *oriP* and copy number and the replication efficiency of EBV episomes, thus contributing to the maintenance of the virus (155).

The nucleocapsid protein of porcine reproductive and respiratory syndrome virus (PRRSV) binds to PARP1, and the interaction is critical for viral replication, since the use of a PARP inhibitor led to inhibited viral growth (156). In an intriguing parallel, Grunewald et al. have shown that the nucleocapsid proteins of both α- and β-coronaviruses are MARylated during infection (157). The function of this modification, and whether it is pro- or antiviral, is currently unknown. Adenoviral core proteins were shown to be ADP-ribosylated, and the use of PARP inhibitors led to greatly reduced infectivity, suggesting a role for the modification in virus decapsidation (158). PARP1 is additionally required for efficient activity of both the H1N1 and H5N1 influenza virus RNA polymerases (159). One study suggests that a poly(ADP-ribose) glycohydrolase (PARG) isoform is degraded as a result of a gene product of herpes simplex virus 1 (HSV-1), which is another indication that PARylation may be beneficial to virulence (PARG counteracts PARylation) (160). In addition, inhibiting PARP activity also inhibits the replication of several types of viruses, suggesting that in these cases, PARylation assists, rather than attenuates, viral replication. This has been demonstrated in several families of viruses, such as herpesviruses, adenoviruses, and arteriviruses (156, 158, 160).

An intriguing role for extracellular PAR was identified by the group of Mitchison (161). PAR was shown to activate cytokine release by macrophages, which is associated with activation of innate immune responses. PAR could be recognized by Toll-like receptors 2 and 4, and inhibition of these receptors prevented cytokine release. Hence, extracellular PAR is a strong proinflammatory signal. This manner of signaling is specific to the polymer, since monomeric ADP-ribose did not elicit a response. Since PAR is primarily an intracellular molecule, it remains to be determined how the extracellular PAR is produced. An extracellular ADP-ribosyltransferase (ART) has previously been identified on T cells, which might function as the source (162). Alternatively, PAR might be released by cells after necrotic cell death.

Several RNA viruses encode macrodomains, which have been described as the "readers and erasers" of ADP-ribosylation (163). These domains recognize and reverse MARylation and PARylation. For example, a macrodomain is conserved in coronaviruses and alphaviruses, as well as other viruses from the *Hepeviridae* and *Togaviridae* families (164–166). Viral macrodomains can remove ADP-ribose or PAR from various protein substrates (167, 168). In addition, PARP10 and PARP14 were induced in response to interferon alpha and to lipopolysaccharide (LPS), suggesting that MARylation is relevant to host-pathogen interaction (169). Since PAR is a regulator of multiple signaling pathways, conserved viral macrodomains are likely used to interfere with one or more host cell antiviral defense mechanisms. Indeed, these proteins mediate resistance to interferon signaling (170), promote virulence, and suppress the innate immune response during coronavirus infection (171–173). Specific protein substrates have been identified for a few macrodomains (169, 174–177), but many remain unidentified to date. Some macrodomains have divergent biochemical activities, such as nucleic acid binding or protein/protein interaction, suggesting that these readers and erasers, like PARPs, are multifunctional (168, 178–180).

Due to the fact that the activity of PARPs has been shown to be both pro- and antiviral, it is clear that a simple definition of the role of PARPs in the response to viral

infection is not sufficient. There are few known enzyme-specific inhibitors of PARPs, which impedes our ability to understand how they respond to viral infections; thus, future work would involve the identification of specific inhibitors for individual PARP family members. Recently, exciting progress has been made in this area (reviewed in reference 181).

PARP and Bacterial Pathogens

Activation of PARP has been observed upon infection of eukaryotic cells by bacterial pathogens. For example, the group A *Streptococcus* (GAS) pathogenicity island encodes streptolysin (SLO) and NAD^+ glycohydrolase. SLO pore formation induced PARP activation, while NAD^+ glycohydrolase activity modulated this PARP activity (182). PARP activation has also been observed in *Helicobacter pylori* infection (183). Bacterial infection was shown to promote PARP activation, through pathways related to inflammation (183, 184).

Interestingly, only a few bacteria have functional PARylation systems, while many have PAR-binding domains, PAR-degrading enzymes, and ADP-ribosylating toxins. These proteins often form operons that may constitute effector systems and may include other domains, such as SLOG, Nudix, and NADAR domains. In parallel to the case for eukaryotic cells, these systems could serve as a source of ATP or intracellular signaling system (185).

Perina et al. performed a detailed analysis of the distribution of enzymes of PAR metabolism in bacteria with sequenced genomes and showed that PARPs are present in six of the 30 known bacterial phyla, where they were probably acquired by horizontal gene transfer (12). Of these, one has been characterized *in vitro*, namely, the PARP from *Herpetosiphon aurantiacus*, which was demonstrated to synthesize polymers (186). The roles of these systems are diverse. In nitrogen-fixing bacteria, the MARylation modification regulates nitrogenase (reviewed in reference 187). In *Bacillus subtilis* and *Streptomyces griseus* ADP-ribosylation contributes to sporulation (188, 189), and in *Streptomyces coelicolor* it regulates antibiotic production (174). The *S. coelicolor* SCO5461 protein was experimentally demonstrated to carry out MARylation.

Plant PARPs

As in animals, plant PARPs are important for DNA damage repair (190–193). Plant PARP2 makes the greatest contribution to DNA repair pathways (194). *Arabidopsis* PARP1 and PARP2 interact physically, and PARP2 is the most important of these in pathogen-induced DNA damage repair and basal resistance (194). Plant PARPs also participate in transcriptional regulation (191, 195).

PARPs also play a key role in responding to abiotic stress and to infection. For example, early studies using PARP inhibition showed that PARP is involved in cell death triggered by DNA damage or oxidative stress (196). PARP was shown to affect stress tolerance (191). Silencing of PARP genes altered stress signal transduction (197). Oxidative stress, drought, and high-light resistance is increased by the knockdown of PARP1 and PARP2 or by the application of PARP inhibitors (191, 198). Thus, the roles of PARPs in responding to abiotic and biotic stress signals appear to differ. Surprisingly, PARP knockout plants were recently found to have constitutive PARP activity and did not exhibit altered stress responses (199). It is possible that this activity could be mediated by the SRO (*s*imilar to *R*CD-one) or RCD (*r*adical-induced *c*ell *d*eath) proteins, which are PARP orthologues that occur only in plants (described below). PARP3, in contrast, can be induced by several factors, particularly during development of the seed (200). PARP3 is a vital component in the storability and viability of the plant seeds (201). Chemical inhibition of PARPs was shown to improve stress tolerance and plant growth, and this correlated with changes in the levels of stress-related metabolites such as anthocyanins (202).

PARP was induced upon *Pseudomonas* infection of *Arabidopsis* (203, 204). Further work showed that PARP inhibition disrupted lignin and callose deposition, which comprise part of the innate immune response, and that pathogen infection activated

PARylation reactions (203). PARylation was shown to regulate genes involved in immune defense (205). Correspondingly, PARPs may be required to repair pathogen-induced DNA damage (206). Most recently, Feng and coworkers demonstrated that PARP2 participates in important reactions with DAWDLE (DDL), a forkhead-associated (FHA) domain protein. The PARylation-dependent interaction between PARP2 and DDL is essential to the function of DDL in plant immunity (207).

Pathogens in turn utilize MARylation and PARylation to antagonize plant cell defenses. Thus, MARylation of plant proteins by bacterial virulence factors was shown to interfere with the plant immune response, especially in pattern-triggered immunity (PTI) signaling pathways (208). For example, the *Pseudomonas syringae* type III secretion system (T3SS) produces ADP-ribosyltransferase effectors that act on plant RNA-binding proteins and kinases (209, 210). The modification of the RNA-binding protein GRP7 inhibits protein function in binding to pattern recognition receptor transcripts (210, 211). HopF2 MARylates kinases in the PTI signal transduction pathway, inhibiting the microbe-associated molecular pattern (MAMP)-induced response. A third effector, AvrRpm1, is predicted to have a PARP-like fold, but its transferase activity is unclear and it may serve to target PARP substrates or binding partners through molecular mimicry (212). Genes encoding other PAR-related functions such as PARG and Nudix hydrolases were also upregulated in response to MAMPs, suggesting the need for a programmed, regulated immune response involving PARPs and the need to avoid excessive consumption of NAD^+ (204).

The RCD (*r*adical-induced *c*ell *d*eath) and SRO (*s*imilar to *R*CD-*o*ne) proteins are PARP orthologues that are found only in plant cells. These proteins contain ART core domains but lack the HYE catalytic triad and are predicted to be inactive; however, this remains to be verified (213). For example, RCD1 does not have detectable NAD binding or PARP activity (213). However, PARP activity has been reported for SRO1 (214). These proteins are regulators of stress responses and plant development (199, 215, 216). RCD1 is upregulated in response to light stress (217). Further, RCD1 interacts with multiple plant transcription factors that control key aspects of plant stress. For example, dehydration-responsive element-binding protein 2 A (DREB2A) is an *Arabidopsis* transcription factor that is involved in the stress response to salt and drought (218, 219). RCD1 binds and destabilizes this transcription factor. Under certain conditions, RCD1 is degraded to increase DREB2A function (219). *Arabidopsis* NAC transcription factors ANAC013 and ANAC046 regulate mitochondrial function (220). RCD1 appears to function in activating a gene expression program of antioxidant response (221).

The SRO1 protein from *Oryza sativa* (rice) and an RNA-binding protein, OsRBD1, conferred tolerance to multiple stresses in a yeast model system (222). These proteins have a domain structure similar to that of human PARP11 in that they contain a WWE domain. The SRO proteins contain an additional, plant-specific domain that is implicated in transcription factor interaction (213, 222). This RST domain has also been identified in the TATA box-binding-protein-associated factor 4 (TAF4) protein, which is found in transcription initiation complexes of eukaryotes (213). Interestingly, the *O. sativa* SRO1c protein mutant exhibited an expression profile and transcription factor interaction profile distinct from those of an RCD1 mutant and also showed impaired cold tolerance (223). Thus, the specific functions of these proteins appear to be quite different from those of PARPs, despite them sharing a common fold of the catalytic domain.

Remaining Questions

Major progress has been made in identifying the involvement and functions of PARPs, PARylation, and MARylation in the response of cells to pathogens. New questions and challenges are opening up in turn. One new hurdle is the identification of PARP substrate proteins, which would provide insight into the signaling pathways that are activated in response to pathogens. Several experimental protocols have been developed (48, 96, 224–226) and more than 2,000 ADP-ribosylation substrate proteins identified to date, and this area is in rapid development (113–117). Recently, new

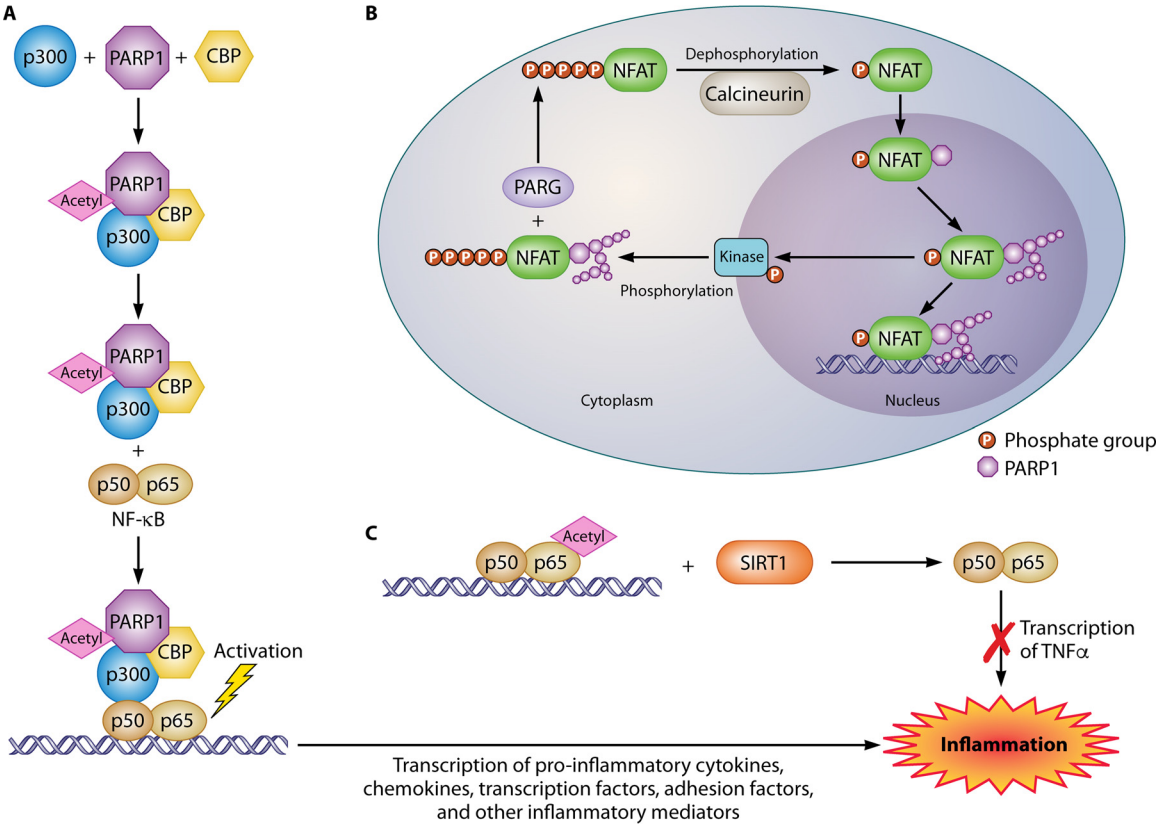

FIG 3 Illustration of selected pathways involved in the stimulation or inhibition of inflammation, which either involve or are related to PARP1. (A) Schematic demonstrating the role of PARP1 in the activation of NF-κB. For activation to occur, there is first binding between PARP1 and two acetyltransferases, p300 and CREB-binding protein (CBP). This binding interaction allows for the acetylation of PARP1 at select lysine residues. The acetylation of PARP1 facilitates a second binding interaction between p300 and the p50 subunit of NF-κB, resulting in the activation of NF-κB. Once activated, NF-κB can bind to DNA and facilitate the transcription of inflammatory mediators (640). (B) Activation of T cells initiates the dephosphorylation of NFAT by calcineurin, which allows NFAT to move from the cytoplasm into the nucleus. Inside the nucleus, NFAT can bind with PARP1, initiating poly(ADP)ribosylation and its interaction with DNA, resulting in the transcription of IL-2. The exit of NFAT from the nucleus back into the cytoplasm is assisted by kinases. The reversibility of PARylation is shown by the depiction of PARG removing the PTM (255, 641). (C) Interaction of NF-κB and SIRT1, both of which are transcription factors shown to be regulated by PARP1. The proinflammatory function of NF-κB is mitigated by a binding interaction with SIRT1, which deacetylates NF-κB, resulting in the downregulation of TNF-α, which has been shown to have an active role in the progression of osteoarthritis (275, 388, 642).

insight has been gained into the nature of PARylation consensus sequences and motifs, which to date has been elusive (96, 227). Further work is required to determine spatial and temporal factors controlling substrate protein PARylation. In addition, we know little about how PARP interactions with substrate proteins and other binding partners are mediated and the ultimate fate of these complexes in the cell. How PARP activity is disrupted in an infected cell can contribute to changes in NAD homeostasis (reviewed in reference 228 and described further below).

PARPs IN INFLAMMATION AND IMMUNITY

PARPs play major roles in inflammatory pathways, promoting inflammatory responses through the expression of cytokines and stimulation of proinflammatory signal transduction pathways. The role of PARP was first established by observing the attenuation of inflammation using pharmacological inhibition of the enzyme (229, 230). Since then, the link between PARP activity and inflammation has been studied extensively. PARP1 regulates the expression of proinflammatory cytokines, enzymes involved in the progression of inflammation, and other proinflammatory gene products (231–234). An overview of inflammatory pathways is presented in Fig. 3.

The proinflammatory actions of PARP1 play roles in pathological processes. PARP1 plays an essential role in the progression of nephritis by the induction of proinflam-

matory cytokines (234) and can participate in the progression of atherogenesis by influencing plaque inflammation (232). Some cytokines, such as IL-6, in turn activate PARP. By stabilizing mRNA and by acting as a transcriptional activator, PARP1 has been shown to play a role in the regulation of inflammatory gene expression (235). It was shown that PARP1 knockout (PARP1$^{-/-}$) mice were protected against several inflammatory disorders (236, 237). Oliver and coworkers demonstrated that when the PARP1–NF-κB binding interaction was inhibited, mice that were PARP1 deficient were less susceptible to inflammation initiated by lipopolysaccharide (LPS) (238).

PARP overactivation leads to inflammation in several tissues; for example, PARP1 activation by DNA damage caused by oxidative stress is believed to play a role in diabetic neuropathy (239, 240). The roles of PARP in inflammation have been studied in several tissues, and its relationship to cancer and obesity has also been found. Induction of inflammation by infection with viruses, fungi, and parasites or by traumatic injury and stroke has been observed (241, 242). PARP hyperactivation has been identified in several central nervous system disorders, including neuroinflammation, neurodegeneration, and ischemia. Extracellular PAR, such as could be released by necrotic cells, was identified as a damage-associated molecular pattern that stimulates inflammatory signaling (161).

PARP as a Transcriptional Coactivator of Inflammatory Pathways

As described above, a major role of PARP in the cell is to act as a transcriptional coactivator/corepressor (87–95). PARP1 regulates the function of transcription factors involved in inflammatory processes, such as activating protein 2 (AP-2), yin yang 1 (YY-1), transcription enhancer factor 1 (TEF-1), octamer-binding transcription factor 1 (Oct-1), Myb-related protein B (B-MYB), specificity protein 1 (SP1), Ets-1, p53, and NFAT (87–95). PARP1 also acts as a coactivator of NF-κB, leading to the activation of inflammatory signaling (243–245).

NF-κB can be activated by the action of PARP1 through various pathways. Under inflammatory conditions, the activation of NF-κB is initiated by the interaction of PARP1 and two transcriptional coactivators that act as histone acetyltransferases (HATs), namely, CREB-binding protein (CBP) and p300. The formation of this complex results in the acetylation of PARP1 at specific lysine residues. The acetylation of PARP1 is required for the PARP1-CBP-p300 complex to interact with the p50 subunit of NF-κB. The binding between p300 and p50 activates NF-κB, initiating the transcription of proinflammatory cytokines, chemokines, transcription factors, and other inflammatory mediators (Fig. 3A) (110, 246, 247).

The interaction of PARP1 with SP1 appears to be proinflammatory, since the PARylation of SP1 resulted in its reduced binding to its consensus sequence. SP1 is normally considered to promote the transcription of anti-inflammatory mediators. However, the interaction with AP-2 could inhibit or activate transcription depending on the conditions (248). In contrast, the high-mobility-group box 1 protein (HMGB1) was shown to be highly PARylated, and this modification enhanced its ability to prevent efferocytosis, an important step in resolving inflammation (249). PARP1 was shown to localize to the promoters of genes responsive to NF-κB. Upon LPS stimulation, PARP1 undergoes cleavage and release from the promoters, increasing the rate of transcription (250). In *Drosophila*, a specific protein, Charon, directs the RelB subunit of NF-κB to promoters through a specific interaction with PARP1 (251). This interaction is required for the transcription of genes encoding antimicrobial defense peptides.

PARP1 was shown to favor the expression of inflammatory chemokines such as IL-1β and TNF-α and enzymes involved in inflammation such as inducible nitric oxide synthase (233, 234, 245, 252). For example, in a model of allergic airway inflammation, PARP was required for the production of Th2-type cytokines such as IL-5, IL-10, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (253). PARP1 plays an important role in the inflammatory response in the brain by regulating the transcription of genes linked to inflammation (93). In addition, PARP induces the expression of cell adhesion molecules such as selectins that favor the influx of white blood cells to tissues.

Thus, PARP is required for the expression of adhesion molecules such as selectins and vascular cell adhesion molecule (VCAM) in atherogenesis (232). Also, PARP1-deficient mice undergo significant transcriptional reprogramming in the colon, with a protective effect in a model of colitis. Analysis of the transcription response showed that the most common gene ontology (GO) types regulated were proteolysis, protein transport, and localization, suggesting that PARP has other functions besides a direct effect on transcription (254). These observations raise the question of tissue-specific PARP functions.

PARP1 also has a proinflammatory function in activated T cells. The interaction of nuclear factor of activated T cells (NFAT) and PARP1 facilitates the transcription of IL-2 (255). Several studies have shown that this process is dependent on the state of phosphorylation of NFAT (255) (Fig. 3B). In inactive T cells, NFAT is heavily phosphorylated and resides in the cytosol. When T cells are activated, calcineurin facilitates the dephosphorylation of NFAT, allowing NFAT to enter the nucleus. In the nucleus, NFAT can bind consensus sequences, either alone or along with other transcription factors. This interaction occurs with the help of PARP1 and the PARylation of NFAT. As a result, PARP1 aids in the transcription of IL-2. Nuclear kinases facilitate the rephosphorylation of NFAT, allowing it to reenter the cytosol.

Other PARP enzymes also play roles in inflammatory processes, some of which may be anti-inflammatory (Table 1). In addition to its antiviral functions in the regulation of stress granule production and maintenance, PARP5b has a proinflammatory function in the progression of cherubism (256). PARP16 participates in the unfolded-protein response (UPR) initiated by the endoplasmic reticulum. PARP16 ADP-ribosylates several proteins and prevents the activation of activating transcription factor 6 (ATF6), thereby linking PARP16 to inflammation (257, 258).

In contrast, PARP10 is a repressor of NF-κB signaling, mediated through binding to K63-linked polyubiquitin and its substrate NEMO (259). PARP10 also acts on a number of other cellular substrates, including glycogen synthase kinase 3B (GSK3B) and other kinases (175).

PARP9, PARP14, and PARP15 form a family originally identified as proteins that were overexpressed in chemotherapy-resistant diffuse large B-cell lymphoma (260). These proteins have been termed the macro-PARPs or the B-aggressive lymphoma (BAL) proteins (260). PARP14, a mono(ADP-ribosyl)transferase, is a specific cofactor of STAT6 that is important in B-cell and T-cell responses. PARP14 regulates the IL-4-mediated proliferation and survival of B cells and is highly expressed in Th17 cells. Inhibition of this protein results in reduced Th17 cell differentiation in a model of allergic airway inflammation (261–263). PARP14 influences the class distribution and affinity repertoire of antibodies in mice and is involved in helper T-cell development (261, 264).

Thus, at least six of the currently known 17 PARPs have demonstrated roles in inflammatory processes, through either participating in transcriptional regulation or other mechanisms.

PARP, NAD^+ Metabolism, and Inflammation

The PARylation and MARylation reaction consumes NAD^+ to produce nicotinamide (NAM) and a modified protein. Hence, the activation of PARP has a major effect on levels of NAD^+ in the cell. Changes in NAD^+ levels can lead to changes in cellular metabolism, homeostasis, and even cell death (reviewed in reference 265). Consumption of excess NAD^+ and ATP upon hyperactivation of PARP was originally thought to lead to cellular necrosis through a cell death process termed as parthanatos (266–268). In this mechanism, PAR acts as a signal to trigger cell death via the release of apoptosis-inducing factor (AIF) from mitochondria (269–272). This is followed by the movement of AIF to the nucleus, which leads to the degradation of genomic DNA and cell death (269–272). NAD^+ levels decrease to as much as 20% to 30% of normal upon DNA damage (273, 274), and conversely, NAD^+ doubles in PARP1 knockout mouse tissue (275). However, recent work has shown that PAR-dependent energy depletion in fact occurs through inhibition of hexokinase, and therefore glycolysis, by PAR produced

by activated PARP1 (276). This inhibition occurs through a specific PAR-binding motif (PBM) on hexokinase. Despite debate over the exact mechanism of parthanatos, it is clear that PARP activation, the activities of other enzymes in NAD^+ metabolism, and cellular NAD^+ levels must all be regulated to avoid deleterious effects.

The importance of NAD^+ homeostasis was originally observed in pellagra, a deficiency of NAD^+ precursors (277; reviewed in reference 228). NAD^+ serves as a coenzyme for numerous enzymes in reduction-oxidation reactions and as an electron carrier in cellular intermediary metabolism. Hence, the loss of NAD^+ homeostasis can lead to unfavorable changes in the cell. The multifaceted roles played by NAD^+ in metabolism have been established through the breadth of its function in various biological pathways (reviewed in reference 278). Decreased cellular NAD^+ levels have been associated with aging (279–283), consumption of a high-fat diet (275, 284), diabetes (279, 285), and stress. These effects are physiologically deleterious, leading to the degeneration of muscle cells (286). The repletion of NAD^+ by providing precursors has been shown to be beneficial in several pathogenic conditions. Nicotinic acid (NA) was shown to be effective in treating dyslipidemia (287); however, side effects were noted, and new derivatives have been developed. Increased NAD^+ levels provided protection against ischemia (288–290) and against neurodegeneration (291). NAM treatment was shown to benefit in a rodent model of obesity and diabetes (285). NAM could also inhibit oxidative damage induced through β-amyloid peptide (292, 293). Repletion using nicotinamide riboside (NR) correlated with improved muscle function, a reduction in protein PARylation, and reductions in inflammation and fibrosis in mouse and *Caenorhabditis elegans* models of muscular dystrophy (294). NR treatment also improved symptoms of diabetes and diabetic neuropathy in a mouse model (295). NR is currently regarded as promising for therapeutics. It has been recently suggested that the key to the selectivity of NAD^+ metabolism is the compartmentalization of intermediates into different subcellular compartments for storage until needed for NAD^+-dependent signaling pathways (278).

Similar effects are observed upon increases in PARP activity given that these enzymes are NAD consumers. Thus, PARP1 activity increases with age and with a high-calorie diet (275, 280, 296), and PARP1 knockout can protect against obesity in mice (275), correlating with the effects of NAD^+ levels. PARP7 activation reduced NAD^+ levels and increased PARylation of proteins in liver tissue (297). Aberrant activation of PARPs can play a role in the neurodegeneration observed in certain disorders involving DNA damage.

In contrast, PARP inhibition increases NAD^+ levels (275, 298) and protects against obesity (275, 298, 299). PARP5 knockout mice had reduced fat and body weight (300) or resistance to diabetes (301). PARP knockout in *C. elegans* led to an increase in life span (296). PARP inhibition also upregulates mitochondrial biogenesis and the unfolded protein response, which could contribute to the beneficial effects toward metabolic disease (298).

Two other classes of enzymes consume NAD^+ and also strongly affect cellular metabolism. The first is the sirtuins or SIR2 family, which are class III histone deacetylase enzymes that function to remove acetyl modifications and other acyl groups from proteins using NAD^+ as a cosubstrate (reviewed in reference 302). These enzymes act on both histone and nonhistone proteins. They function to stimulate oxidative metabolic pathways in mitochondria, improving resistance to oxidative stress (reviewed in references 265 and 303). Through this mechanism, they favor increased life span in multiple organisms, such as yeast, *C. elegans*, *Drosophila*, and mammals (304–310). Their action benefits symptoms of inflammation and aging-related diseases such as cancer and cardiovascular disease. In mammals, they hold a broad spectrum of biological roles in cellular processes and pathways that can be attributed to the cellular localization of the seven sirtuin family members. Through their influence on the cell cycle, apoptosis, and metabolism, they have emerged as important regulators of cancer cell proliferation and tumorigenesis (reviewed in references 311 and 312). Several sirtuin enzymes also exhibit ADP-ribosyltransferase activity, which is less efficient than their deacetylase

activity. The physiological importance of this enzyme activity has been debated, but it may influence DNA repair (313) and enzyme activities (314). Microbial sirtuins have been identified mainly in pathogenic bacteria and fungi and termed SirTMs or class M sirtuins (315). This class of enzymes exhibit more efficient ADP-ribosylation than mammalian sirtuins and may take advantage of this activity as part of a regulatory response to oxidative stress, such as during engulfment by host cells (315).

In mammalian cells, SIRT1 is found predominantly in the nucleus to remove acyl groups from histones and a number of cellular targets (316). The action of SIRT1 is protective against osteoporosis, acting as a positive regulator of bone mass in mice (317, 318). This may be mediated by forkhead transcription factors of class O (FoxO) proteins (319) or under inflammatory conditions, through negative regulation of NF-κB signaling (320, 321). In addition, SIRT1 action protects against other aging-related and neurodegenerative diseases, including Alzheimer's disease (322–326). Recently, protection against neurodegenerative diseases and promotion of stem cell differentiation were reported (327–329). SIRT1 deacetylation of p53 protected against neuronal cell apoptosis in a model of diabetic cognitive impairment (330). SIRT1 contributed to memory enhancement in healthy animals and in Alzheimer's disease models, through the regulation of neurotrophic factors, enhancement of tau degradation, and additional mechanisms (331).

SIRT1 function has also been shown to be strongly associated with cancer and apoptosis (reviewed in reference 332). SIRT1 gene polymorphisms were shown to assist in compensating for oxidative stress during aging (333), to affect gene expression in cardiovascular disease (334), and to affect obesity, fat and cholesterol metabolism, and high blood pressure (335–337).

SIRT2 can be found predominantly in the cytoplasm but is also present in the nucleus during certain points in the cell cycle, where it deacetylates histone substrates and cell cycle checkpoint kinases (338, 339). In mammals, this protein is highly expressed in the brain (340). Like SIRT1, SIRT2 is upregulated during calorie restriction and downregulated under conditions of energy excess (341, 342). Recent applications to its function as a deacetylase of microtubules link it to aging brains and neuroprotective effects (343). In addition, SIRT2 acts to suppress inflammatory signaling through NF-κB deacetylation. SIRT2 regulates several proteins important in metabolic regulation and homeostasis, particularly lipid metabolism and regulation. SIRT2 suppresses adipogenesis, inhibits adipocyte differentiation by deacetylating FoxO1, and stimulates the degradation of ATP-citrate lyase, a key enzyme in hepatic lipogenesis (344–346). There are also roles in insulin signaling and metabolism (340).

SIRT3 to -5 are localized primarily to mitochondria and have been implicated in oxidative stress responses (347–350). SIRT3 acts as a tumor suppressor through the regulation of reactive oxygen species (ROS) (351). SIRT3 also activates FOXO3a, a regulator of ROS in the heart and negative regulator of cardiac hypertrophy (352). On the other hand, SIRT3 was also shown to have an oncogenic role under some circumstances. SIRT3 is essential for maintaining mitochondrial function and is overexpressed in head-and-neck squamous cell carcinoma (HNSCC) (353), where it contributes to cell growth and survival (354, 355). SIRT3 may prevent cells from undergoing apoptosis under stress conditions (356), antagonize p53 growth arrest (357), and induce resistance to anticancer agents (358). A SIRT3 inhibitor was able to enhance apoptosis of HNSCC cells (359), likely by disrupting the ROS balance, supporting SIRT3 as a useful therapeutic target for this type of cancer.

SIRT4 and SIRT5 have multiple enzymatic activities; for example, SIRT5 cleaves succinyl, malonyl, and glutaryl groups in preference to acetyl groups (360). SIRT4 was shown to have lipoamidase activity that negatively regulates the pyruvate dehydrogenase complex (361, 362). Like SIRT3, SIRT4 may contribute to tumor suppression or tumorigenesis depending on conditions. SIRT4 also participates in DNA damage response pathways and contributes to genome stability, thus contributing to tumor suppression (363, 364). However, SIRT4 was also shown to be involved in cellular stress responses, is induced by stress, and contributes to cell survival and growth under stress

conditions (365). In this manner, SIRT4 has been implicated in oncogenic transformation and may contribute to survival and drug resistance of cancer cells (365).

SIRT5 is specific for negatively charged acyl groups, especially succinyl, malonyl, and glutaryl groups (360, 366). This activity regulates the activity of mitochondrial enzymes such as the pyruvate dehydrogenase complex, succinate dehydrogenase, and carbamoyl phosphate synthetase 1 (367–369). This impacts diverse metabolic pathways such as glycolysis and the urea cycle.

SIRT6 is localized in the nucleus, where it helps to maintain genome stability and telomere function by histone deacetylation (370). Recent findings support its ADP-ribosylation of PARP1 under oxidative stress to assist in the repair of DNA (313, 371–374). SIRT6 acts as a tumor suppressor and participates in genome maintenance (370). SIRT6 is also able to cleave long-chain fatty acyl groups such as myristoyl and palmitoyl, allowing it to regulate the secretion of tumor necrosis factor alpha (375). SIRT7 resides in the nucleus and participates in transcription (376). This protein has been identified as an oncogene through its activity in transcriptional repression (377), association with the transcription factor ELK4 (371), and selective H3K18 deacetylation activity, which has been linked to oncogenic transformation (371, 378–381) and aggressive cancers (378, 379). SIRT7 participates in DNA double-strand break repair and is involved in genome integrity maintenance and nonhomologous end-joining repair (382). However, much of its catalytic activity may still be unknown. The breadth of functions of this family of enzymes has made them promising drug targets.

PARPs and sirtuins regulate each other in a complex manner. PARP2 acts as a transcriptional repressor of SIRT1 expression (275) and negatively regulates the SIRT1 promoter. By efficiently consuming NAD, PARP1 limits SIRT1 activity (275, 293, 383, 384). In contrast, SIRT1 inhibits PARP1 through its deacetylation activity and through transcriptional regulation. Increased PARP activity was observed in SIRT1 knockout cells (384, 385). PARP1 knockdown (pme-2 knockdown) in worms led to increased Sir2 activity as well as longer life span and increased NAD^+ concentration (386). While PARP1 is a transcriptional coactivator of NF-κB and favors inflammatory processes, SIRT1 inhibits NF-κB activity by deacetylating the protein (387). SIRT1 interacts with NF-κB, resulting in the deacetylation of the latter and in the inhibition of TNF-α (Fig. 3C) (275, 388). SIRT1 and PARP1 are connected through their use of the substrate NAD^+, and both are able to modify histones. The two enzymes participate in antagonistic cross talk due to their competition for the NAD^+ substrate (383). Many cellular functions are likely to be regulated by SIRT1/PARP1 reciprocal regulation.

The other important consumer of NAD^+ that strongly affects overall cellular NAD^+ levels is the CD38/CD157 protein, an enzyme that produces the second messengers ADPR and cyclic ADP-ribose (cADPR) from NAD^+ (389). In contrast to sirtuins, whose activity is affected by low levels of NAD^+, CD38 plays an active role in depleting NAD^+ (390). For example, cells overexpressing CD38 showed decreased [NAD^+] together with decreased expression of antioxidant proteins, likely due to reduced sirtuin activity (391). As an effect of this metabolism, CD38 knockout mice showed improved resistance to glucose intolerance and diet-induced obesity (392, 393). This correlated with increased [NAD^+] in multiple tissues and increased sirtuin activity (392, 394). The roles of ADPR and cADPR as second messengers have been reviewed (395–397). CD38 is a multifunctional transmembrane glycoprotein and, in addition to its role in producing cADPR, also regulates Ca^{2+} flux in the cytoplasm (398, 399). CD38 participates in other signal transduction pathways such as insulin secretion (400, 401). CD38 assists in B-cell differentiation and leukocyte adhesion and proliferation (402, 403) and associates with lipid rafts (404, 405).

CD38 expression has also been shown to correlate with aging. Overexpression of CD38 in cancer cells leads to the development of senescence (406). CD38 inhibits the function of SIRT3 in the mitochondria by affecting levels of NAD^+ (390). CD38 expression is induced by inflammatory cytokines and interferon (407, 408), which also increase during aging (409–413), suggesting a possible reason for CD38 increase during the aging process (414).

As a result, CD38-inhibitory therapy is an area of interest for metabolic dysfunction related to age (415). Specific CD38 inhibitors have been developed (416–420). Several inhibitors were shown to have the ability to raise NAD levels and improve glucose homeostasis and fatty acid metabolism *in vivo* (417, 420). CD38 was shown to play a role in certain diseases related to aging, including Alzheimer's disease (421).

CD38 is overexpressed on cells of some hematologic malignancies (422–426) and has been proposed as a therapeutic target for myeloma and for T-cell acute lymphoblastic leukemia treatment (405, 427). Recently, it was suggested that CD38 may be a biomarker of resistance to certain cancer therapies, and it was effectively used as a secondary target in combinational therapies for lung cancer (428). CD38-expressing cells promoted tumor growth in a murine model of esophageal cancer (429). Its effect on mitochondrial function led to an enhancement of proliferation and inhibition of apoptosis in cervical cancer cells (430). Conversely, CD38 knockout led to suppression of tumorigenesis in a lung cancer model (431), and CD38 overexpression was identified in patient samples. This suppression occurred both in wild-type mice and in an ARH1-deficient background; ARH1-deficient mice are already prone to tumor development (described above).

A monoclonal antibody directed against CD38, termed daratumumab, has been approved for the treatment of multiple myeloma (432). This antibody was originally developed using a panel of CD38-specific monoclonal antibodies generated from human antibody transgenic mice (433). The antibody exhibited high efficacy in an animal model of multiple myeloma (434). CD38 has also been developed as a target for positron emission tomography (PET) imaging using daratumumab antibody (435, 436). Other antibodies, such as MOR202, a human antibody, and isatuximab, a humanized antibody, are in various stages of clinical trials (437, 438). CD38 expression has also been associated with HIV infection, where CD38 expression was noted on HIV-specific $CD8^+$ cytotoxic T cells (439, 440), and with autoimmune disease (441), where clinical applications are also possible.

NAD^+ Metabolism and Infection

NAD^+ is an essential cofactor and substrate for bacterial cellular metabolism, and pathogenic bacteria have evolved to exploit NAD^+ and PARP pathways. Group A *Streptococcus* (GAS) possesses a NAD^+ glycohydrolase that cleaves NAD^+, yielding NA, ADPR, and cADPR, which drastically decreases NAD^+ and ATP concentrations and leads to cell death. This leads to a significant reduction in innate immune system responses, and protects GAS from autophagy (442) and lysosome acidification (443), and leads to a reduction in PARP activity. The reduction in PARP activity is believed to stimulate the release of high-mobility-group box protein 1 (HMGB1) from the nucleus to the cytosol, where it acts as an inflammatory mediator (444), is deposited in damaged tissues (445), and contributes to necrosis. Conversely, NADase-negative GAS is also able to activate PARP, by an unknown mechanism.

A few other bacterial pathogens also activate PARP upon infection. Thus, *H. pylori* infection activates PARP by PARylation (183). *H. pylori* infection triggers apoptosis via the caspase-independent AIF pathway (446) and programmed necrosis (447). Bacterial infection was shown to promote PARP activation, through pathways related to inflammation (183, 184).

Various pathogens exploit PARP activity to promote conditions favorable to growth and virulence. In contrast, *Chlamydia trachomatis* infection led to the degradation of PARP1 through the action of a specific bacterial enzyme, chlamydial protease-like activity factor (CPAF) (448), and this was associated with the inhibition of HMGB1 release from the nucleus along with degradation of HMGB1 (449). This would lead to a reduced inflammatory response. CPAF is downregulated during persistent infection, allowing PARP1 activation and HMGB1 release (450). Chronic inflammation thus may be observed during persistent disease.

NAD^+ production through the activity of the indoleamine 2,3-dioxygenase (IDO) enzyme has been shown to assist the clearing of pathogenic infections. For example,

IDO induced by IFN-γ inhibited the replication of *Staphylococcus aureus* (451), and $CD4^+$ T cells inhibited the growth of *Mycobacterium tuberculosis* by sequestering tryptophan, the precursor to NAD^+ (452). It should be noted, however, that some pathogens are NAD^+ auxotrophs and require NAD^+ obtained from the host cell to replicate. For example, *Borrelia burgdorferi* and *Brucella abortus*, both intracellular pathogens, produce nicotinamidases that convert NAM to nicotinic acid (NA), a precursor to NAD^+ in the Preiss–Handler pathway (453, 454). *Haemophilus influenzae* lacks the Preiss-Handler pathway for NAD biosynthesis and requires NMN and NR as precursors (455–457). Structural data for *H. influenzae* NAD nucleotidase (NadN), a periplasmic enzyme, have suggested a novel mechanism for the synthesis of NAD^+ that involves its hydrolysis to NR, adenosine, and phosphate, followed by uptake of NR across the inner membrane and resynthesis via the NadR enzyme. A significant conformational change is involved during catalysis, which suggests likely avenues for inhibitor development (457). These enzymes are also found in other bacteria and in parasites such as *Leishmania*. In *Leishmania*, knockout of the enzyme led to a significant decrease in NAD^+ content and a reduction in virulence (458). The *Leishmania* parasite was shown to increase intracellular NAD levels once present in the cell (459).

Role of PARG

Damage to strands of DNA activates repair pathways, which involve PARPs, to the site of repair, where the synthesis of PAR polymers is often prompted. This biochemical reaction is regulated by an enzyme known as poly(ADP-ribose) glycohydrolase (PARG). The reversibility of the ADP-ribosylation reaction is shown through the action of PARG, which hydrolyzes the PAR polymer (460). PARG activity is primarily responsible for the degradation of PAR polymers whose mass accumulation is metabolically harmful to the cell, as described above (461). In addition to the disruption of NAD^+ metabolism, excessive PARP activity and PAR production could have unpredictable effects on RNA-binding and DNA-binding proteins through competition for binding (462) and could cause the dysregulation of cellular organelle assembly and stability (463).

PAR polymers produced upon DNA damage are short-lived, with a half-life of less than 1 min. This is in contrast to constitutively produced polymers, which are longer-lived, with half-lives of ~8 h (464–468). The degradation of PAR polymers occurs specifically at glycosidic bonds by hydrolysis and yields free ADP-ribose (469). PARG production is regulated by a single gene, producing a protein which is approximately 110 kDa with a C-terminal catalytic domain (470–472). While full-length PARG remains in the nucleus, shorter isoforms are also present and are distributed predominantly in the cytoplasm (473–475). These isoforms vary not only in size but also in the way in which they are activated by biological events such as apoptosis or proteolysis of their posttranslational modifications (PTMs). PARG nuclear localization increases upon DNA damage, presumably in response to the high level of PARylation produced by PARPs (476, 477).

Though PAR is integral to the regulation of cellular death pathways, the role of PARG was not well understood. Recently it has been demonstrated that following a lethal dosage of the alkylating agent *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) to HeLa cells, PARP1 directly interacts with PARG, even in the absence of NAD^+ or PAR, facilitating nonapoptotic cellular death pathways (478). A role of PARG in apoptotic cell death has also been suggested. It is thought that the preferential binding of DNA repair factor XRCC1 to PARylated PARP1 to help facilitate repair displaces PARG from PARP1, which triggers a cascade of apoptosis. (272, 478).

PARG has further been demonstrated to be necessary for cell survival in murine models, where the absence of PARG in embryonic cells proved to be lethal (461). However, in other studies, the absence of PARG was not shown to be essential for survival in the absence of genotoxic stress, which suggests that stress plays a pivotal role in PARG activity (479–481). This has been supported by studies showing that in the presence of genotoxic stress, cells lacking PARG exhibited increased cell death in addition to the nonrepair of single- and double-strand DNA breaks (482–484). In

response to replicative stress conditions, PARG is pivotal in regulating the mass accumulation of PAR, arresting the collapse of replication forks and the development of additional DSBs (480).

PARG was shown to be integral to the growth of *Trypanosoma cruzi* epimastigotes, and PARG inhibition caused changes to the cell cycle in the parasite. Knockdown of host cell PARG also abrogated *T. cruzi* infection (485). In *Trypanosoma brucei*, PARG knockdown led to increased sensitivity to oxidative stress (486). Hence, PARG functionality is also essential for establishing trypanosomal infection.

A strong case can be made for the importance of the biomedical implications of the inhibition of PARG in the field of cancer therapy. For example, the absence or inhibition of PARG has been shown to arrest the metastasis of cancer cells in the human colon and in murine models, the death of BRCA-2 tumor cells (487, 488), and cell death of homologous repair-deficient tumor cells (489). PARG silencing led to a reduction in PARP expression and a decrease in signaling through the phosphatidylinositol (PI) 3-kinase/Akt pathway, mediated through a reduction in NF-κB (487).

The inhibition of binding between PARG and the human antigen R (HuR) RNA-binding protein helps to improve PARP inhibition therapy in pancreatic cancer cells (490). Another study presented work demonstrating that the inhibition of PARG helped to reduce the negative effects of cellular exposure to benzo[*a*]pyrene, a polycyclic aromatic hydrocarbon known to induce carcinogenesis (491, 492).

The focus of PARG inhibitor therapy for cancer can be attributed to the role it has in DNA repair, like PARP1, -2, and -3. Importantly, PARG is encoded by a single gene, in comparison to the 17 human PARP genes. As a result, all isoforms of PARG have a conserved catalytic domain, which offers a more direct target for inhibitor development (493). It has been demonstrated that PARG inhibitors offer unique pharmacological effects in comparison to olaparib, the first PARP inhibitor to be accepted by the FDA (494–496). Several PARG inhibitors, both synthetic and natural, have been identified; however, their wide use is limited by problems with toxicity and cell permeability (497–499). Four specific inhibitors of PARG, ADP (hydroxymethyl)pyrrolidinediol (ADP-HPD), mono-galloyl glucose, rhodanine-based PARG inhibitor 2 (RBPI-2), and salicylanilide, have increased specificity to PARG and have been used extensively to help uncover the breadth of the biological role of PARG inhibitors (488, 500–503). Recently, new smaller inhibitors, known as phenolic hydrazide hydrazones, have been synthesized and shown to be effective inhibitors of PARG *in vitro*, with 50% inhibitory concentration (IC_{50}) values in the micromolar range (504).

The role of PARG in DNA repair has helped to highlight its potential as a target for inhibitor development. To date the primary focus of PARG inhibitor research has been in cancer therapy; thus, more research investigating the additional applications of PARG inhibitor therapy is needed. Work on PARG inhibition against infection is in the preliminary stages but is also promising.

MARylation and Its Reversal

MARylation is a common mechanism used by bacterial toxins to interfere with host cell metabolic and regulatory pathways. ADP-ribosylating toxins transfer an ADP-ribose moiety to amino acids such as arginine, cysteine, and asparagine to acceptor proteins in the host cell, destroying enzyme activity. This activity is shared by a family of proteins including cholera toxin, diphtheria toxin, pertussis toxin, and others (10). These toxins are structurally and functionally related to the PARP enzymes (505). In addition to the modifications carried out by pathogens, these PTMs are also exerted by host cell PARPs for numerous regulatory functions, as has been described above.

MARylation cannot be removed by PARG, and its reversal requires other enzymes (186). Instead, mono(ADP-ribosyl) units are acted on by two other classes of enzymes, namely the ADP-ribosylhydrolases (ARHs) and the macrodomains. The former are homologues of the dinitrogenase reductase-activating glycohydrolase (DraG). In humans, three ARHs are expressed and have functions that are yet to be fully understood.

Though ARH2 is thought to be catalytically inactive (506–508), the other two enzymes are active in the hydrolysis of the ADP-ribosylation modification.

ARH1 is a site-specific hydrolase of MARylated proteins at arginine residues (509). This enzyme plays a role in the suppression of tumorigenesis through regulating cell proliferation and the cell cycle (510). ARH1 mutants or knockout cells with low enzyme activity were tumorigenic, and ARH1 mutants identified in the human cancer database localized to the enzyme catalytic site (511). Importantly, ARH1 knockout mouse cells could not hydrolyze MARylated arginine, showing that ARH1 is the only cytoplasmic enzyme able to degrade this PTM (512). The enzyme also plays a role in the response to cholera toxin. Cholera toxin is an ADP-ribosylating toxin that acts on the α subunit of the Gs protein (Gsα, a binding partner of adenylate cyclase). Activation of adenylate cyclase leads to increased cellular cyclic AMP, ion efflux from the cell via the cystic fibrosis transmembrane regulator (CFTR), and fluid loss from the intestine. In ARH1 knockout mice and fibroblasts, MARylation of Gsα was increased and was longer lasting, together with increased fluid accumulation in the intestine (512). These observations suggest that ARH1 is important in the host cell response to cholera toxin.

ARH3 catalyzes primarily exolytic activity, acting mainly at terminal sites of PAR chains and on MARylated serine residues. Its activity varies from that of PARG, in that it site specifically hydrolyzes PAR at chain termini, by a Mg^{2+}-dependent mechanism, to yield ADP-ribose (513). Two amino acids, D77 and D78, are critical for hydrolase activity (506–508). An important physiological role of ARH3 is to protect cells from parthanatos and to regulate PAR degradation in both the nuclei and cytoplasm (499). Thus, oxidative stress stimulates increased PAR synthesis by PARP1 and PAR cleavage by PARG in the nucleus. PAR is translocated to the cytoplasm through nuclear pores and releases mitochondrial membrane-associated AIF, which initiates parthanatos (269–272, 514). ARH3 then acts to modulate the level of PAR by degrading these free chains, starting at chain termini, after they have been translocated. Thus, ARH3 is important in modulating and protecting cells from parthanatos (499).

ARH3 is also able to cleave proteins that are MARylated on serine residues. This activity has been observed in human cancer cells (515, 516). Serine ADP-ribosylation is a widespread and important PTM, appearing after DNA damage on histones (225, 517, 518) and high-mobility group proteins, DNA repair factors, and other proteins (519, 520). The sequence motifs KS and RS were shown to identify substrate proteins (516). The activity of ARH3 is interesting in that it has no activity in hydrolyzing ADP-ribose from arginine, cysteine, diphthamide, or asparagine bonds (506, 508, 521). ARH3, rather than PARG, is responsible for mitochondrial PAR degradation, suggesting a function related to PAR or *O*-acetyl-ADP-ribose (OAADPR) metabolism in the mitochondria (522).

Both ARH1 and ARH3 are able to degrade OAADPR produced by sirtuins (507). OAADPR participates in ion channel gating (523), redox metabolism (524), chromatin regulation (525, 526), and gene silencing (525). Therefore, ARH3 has a role in signal transduction involving both PAR and OAADPR (reviewed in reference 527).

It is also known that some macrodomain proteins have the ability to degrade the ADP-ribosyl modification. The macrodomain proteins terminal ADP-ribose protein glycohydrolase (TARG1), MacroD1, and MacroD2 degrade mono(ADP-ribose) at glutamate and aspartate residues. TARG1 degrades MAR by a different mechanism than PARG, by breaking the ester linkage between PAR and glutamate, an action that cannot be accomplished by PARG (186). MacroD1 exists primarily in the mitochondria and has low specificity in its ADPR hydrolase activity, removing a broad spectrum of ADP-ribosyl moieties with ester linkages from proteins, DNA, and small molecules (528). MacroD2, in addition to its ADP-ribosylhydrolase function, acts mainly in the cytoplasm, where it selectively deacetylates *O*-acetyl-ADP-ribose (529). Several macrodomain proteins have also been identified as degraders of PAR.

It has been shown biochemically, structurally, and phylogenetically that viral and cellular macrodomains are closely related (530). Therefore, it is not surprising that viral macrodomains also have the ability to degrade ADP-ribosylation. Most macrodomains from viruses belong to the MacroD class and are characterized by their ability to

remove the entire PAR modification, similarly to TARG1 (167). The nsP3 macrodomain from chikungunya virus can hydrolyze the MAR modification from aspartate and glutamate, but not lysine, residues (171). Mutant viruses with reduced hydrolase activity showed lower virulence in mice and slower replication in mammalian cells; mutants with no activity were unable to replicate at all in mammalian or mosquito cells. Therefore, this macrodomain is essential for viral replication, in both the host and the insect vector, and for virulence (171).

It is believed that viral macrodomains can remove the MARylation and PARylation modification (167). The *Hepeviridae*, *Togaviridae*, and *Coronaviridae* families of viruses express conserved macrodomain proteins (531–539). Many of these macrodomains exhibit ADP-ribosylhydrolase activity (171, 538, 540, 541). Macrodomain mutations that reduced nsp3 ADP-ribosylhydrolase activity *in vitro* also led to a reduction of viral load in infected mice and protected mice from an otherwise lethal severe acute respiratory syndrome coronavirus (SARS-CoV) infection (173). This was attributed to changes in the innate immune response, including an enhanced interferon and proinflammatory cytokine response. These observations show that the SARS-CoV macrodomain is involved in suppression of the innate immune response and cytokine repression and is important for virulence (173). Its exact molecular target(s) is currently unknown. In mouse hepatitis virus (MHV), the conserved macrodomain is required for induction of liver disease and production of the inflammatory cytokines TNF-α and IL-6 (542). A subsequent MHV study using a macrodomain point mutant showed a drop in viral titer, cytokine and chemokine expression, and virulence with respect to those with the wild type, supporting the role of the macrodomain in virulence and interaction with the innate immune system (172). Other work demonstrated that mutant viruses of SARS-CoV and human coronavirus 229E (HCoV-229E) lacking macrodomain activity were highly sensitive to interferon and showed an unusual cytokine induction pattern and slower growth, also suggesting participation of the macrodomain in resistance to the innate immune system (170).

It has been suggested that macrodomain activity may antagonize the antiviral effects of ADP-ribosylation (157). Most macrodomains possess conserved primary sequences, but some subclasses lack sequence conservation, resulting in novel functions. For example, *Mycobacterium tuberculosis* expresses a non-macroD-type macrodomain which has the ability to remove ADP-ribosylation from DNA rather than proteins. In addition, it acts as an antitoxin to a mycobacterial toxin that ADP-ribosylates DNA at specific thymidine residues (543). Coronaviruses encode additional macrodomains that interact with guanine quadruplexes (168, 544) and target host cell p53 for ubiquitylation and degradation by stabilizing the accumulation of the E3 ubiquitin ligase RCHY1 (178, 180). This domain is important in the replication of the viral RNA genome (178). It is presently unclear whether the ADP-ribosylhydrolase function is shared by these divergent domains.

Role of PARP in Inflammatory Autoimmune Disorders

PARP inhibitors are presently being explored as therapeutics to prevent cell death, tissue damage, and dysfunction associated with aging or oxidation damage-related pathologies, such as cardiovascular disease, stroke, autoimmune and inflammatory disease, and diabetes. Reactive oxygen and nitrogen species are generated in cardiomyocytes and endothelial cells during ischemia/reperfusion injury, cardiovascular aging, and diabetic complications. These reactive species induce oxidative DNA damage and consequently activate PARPs (545). The effects of PARP inhibitors on inflammatory responses may contribute to their therapeutic effects in cancers (546). Many cancer cells display dysfunctional DNA repair, and PARP inhibition can assist in preventing cellular replication (547). PARP inhibitors can play a crucial role in the treatment of both BRCA-negative and -positive cancers and can be effectively used as therapeutics for prostate, ovarian, and breast cancer. These applications have been reviewed elsewhere (548).

PARP inhibition has positive effects on inflammatory responses. Results published by Garcia and coworkers in 2008 demonstrated that the inhibition of PARP1 reduced the expression of proinflammatory cytokines (549). Inhibition of PARP1 repressed the production of proinflammatory cytotoxic cytokines and enhanced the production of anti-inflammatory cytokines (550–553).

PARP inhibitors were tissue-protective in animal models of multiple sclerosis, meningitis, arthritis, stroke, and traumatic brain injury (241, 554–560). PARP inhibitors reduced neuroinflammation, edema, leukocyte infiltration, and the expression of adhesion proteins (242). PARP inhibition in leukocytes reduced inflammation via effects on the cytoskeleton and reduced leukocyte adhesion and migration across the blood-brain barrier (BBB) (561). PARP inhibitors protected the BBB and reduced its permeability in *in vitro* and *in vivo* models of inflammation (557). PARP1 inhibition was also protective in a model of pancreatitis and reversed chronic liver injury and fibrosis (562). Studies conducted on PARP1 knockout mice further suggest that inhibitors of PARP are a preventative therapy against inflammation, since the activation of PARP mediated the progression of symptoms associated with hemorrhagic shock, such as lung inflammation and heart failure (563).

PARP inhibitors are in development for treatment of other inflammatory conditions. Specific roles are seen in rheumatoid arthritis (RA), Graves' disease, and Huntington's disease. Two PARP polymorphisms were identified as effective in the treatment of Graves' disease and Graves ophthalmopathy (564). PARP1 inhibition was also protective in animal models of diabetic retinopathy and of Huntington's disease (239, 565, 566).

Arthritis

Considered an autoimmune disease, rheumatoid arthritis (RA) is characterized by inflammation occurring in the joints and surrounding tissue. This results in the deterioration of the joint cartilage as well as the erosion of bone. This disease is observed in all populations worldwide; however, there is no clear pathogenic pathway which has been identified (567). In a collagen-induced arthritis (CIA) model, PARP1$^{-/-}$ mice showed lower levels of proinflammatory cytokine expression (568). This was corroborated by studies in patient-derived cells (549). In mouse models, PARP inhibition resulted in a reduction in the onset of the disease (569–571). Thus, Kröger and coworkers demonstrated that the combination usage of a PARP inhibitor and thalidomide, an inhibitor of tumor necrosis factor, had synergistic actions, resulting in the successful inhibition of PARP (571). Inhibition of PARP arrested the progression of previously established cases (571). 5-Iodo-6-amino-1,2-benzopyrone (INH_2BP), a novel PARP inhibitor, showed positive dual effects on both the onset and the severity of the disease (572). In addition, it is known that there is a positive correlation between the phorbol ester-activated burst of white blood cells and the onset and progression of arthritis (567, 570). When PARP activity was inhibited, the development of arthritis was prevented.

PARP inhibitors, in conjunction with small interfering RNA (siRNA) technology, have provided strong positive results in the treatment of RA (573). One factor that creates concern is the possibility of DNA mutation acceleration due to long-term PARP inhibition. However, PARP inhibitors are well tolerated by patients, and it is possible that without aggressive treatment the inflammation in the joints can be treated successfully with the application of dosages within human tolerance.

Lupus

Systemic lupus erythematosus is an autoimmune disease that is characterized by widespread inflammation. Both heredity and environmental factors have been identified as possible contributors (566). Abnormal metabolism of PARP has a role in the development of lupus (574). There is a decrease in the synthesis of PARP in the leukocytes of patients diagnosed with lupus, which may be a result of a defect in the transcription of the gene (574). In addition, there is an elevation in the levels of anti-PARP and anti-PAR autoantibodies found in patients (575, 576).

Hyperthyroidism (Graves' Disease)

Graves' disease is an autoimmune disease which is associated with hyperthyroidism. The circulation of antibodies which mimic the thyroid-stimulating hormone (TSH), by binding to and activating the substrate, contribute to pathogenesis. Several genes and environmental factors have been identified (577). Polymorphism of PARP1 may be a contributor to the development of Graves' disease (564, 578, 579).

PARP STRUCTURE AND INHIBITION

PARPs are characterized by the presence of the PARP signature sequence and a β-α-loop-β-α NAD^+-binding fold. This sequence is not conserved equally among the members of the PARP family, accounting for variations in catalytic function. There are several other structural variations among the members of the PARP family. This variation accounts for similarity in the catalytic activity along with the versatility of their biological roles, cellular locales, binding partners, and substrate proteins. The most current understanding of the domain structure of the 17 human PARP proteins is illustrated in Fig. 1.

The PARP Signature Sequence and Its Significance

The PARP signature sequence is responsible for ADP-ribosyltransferase activity. It is composed of 70 to 100 amino acids and includes the NAD^+-binding site. The catalytic activity of PARPs (resulting in PAR formation) occurs when the ADP-ribose moiety of NAD^+ is transferred to the target protein, with the release of nicotinamide. Catalysis can be attributed to the NAD^+-binding pocket, formed by β sheets and α helices, between a conserved Glu residue on one side and His on the other. NAD^+ binding is stabilized by a hydrogen bond between His and the O2′ hydroxyl of the adenosine ribose (580). Catalysis is assisted by the HYE triad, which consists of H862, Y896, and E988 (PARP1 numbering). In the triad, the glutamate residue acts as a general base, while the histidine assists in orienting NAD^+ for nucleophilic attack and stabilizing the transition state and the tyrosine assists in NAD^+ binding (580–582). The catalytic site of the PARP1 ART domain in the presence of an effective inhibitor, olaparib, is shown in Fig. 4A. Olaparib interacts with two residues of the catalytic triad, H862 and Y896, and forms hydrophobic interactions and hydrogen bonds with other residues in the binding pocket (583, 584). Inhibitor classes are discussed further below.

The DNA-binding domain of PARP1 consists of tandem repeat zinc finger domains which bind to DNA and activate the catalytic domain (585). A study by Ali et al. revealed the crystal structure of the human PARP1-DBD bound to a DNA break. ZnF1 and ZnF2 domains of multiple PARP1 molecules form a DNA break-sensing module (586). An alternate mechanism suggests that DNA damage can also be detected by monomeric PARP1, through cooperative action of flexibly linked ZnF1 and ZnF2 domains. This mechanism proposes that the binding of ZnF2 positions ZnF1 via a fly-casting process (587, 588). PARP1 "reels in" protein domains in the same molecule by binding to DNA, triggering PARylation by unfolding an inhibitory HD subdomain (584, 587). Activation by DNA binding triggers the automodification of PARP1.

The central region of the enzyme contains a BRCT (breast cancer type 1 susceptibility protein [BRCA1] C-terminal) motif, which is involved in protein-protein interactions (589). It is suggested that automodification in this domain and nearby causes the release of DNA repair proteins required for the processing and repair of nicks. Automodification reduces affinity for intact chromatin but not for nucleosomes with exposed DNA ends and may cause PARP1's release of DNA and convert PARP1 to a histone-binding protein (86).

Coupling DNA Damage Detection to Catalytic Activity

Langelier et al. reported that upon binding of PARP1 to a DNA break, the domains collapse together, establishing interdomain contacts that distort the structure of the helical domain (HD) (590). When in complex with DNA, partial unfolding and destabilization of the HD occur, and this underlies PARP1 activation (590) (Fig. 4B). In contrast

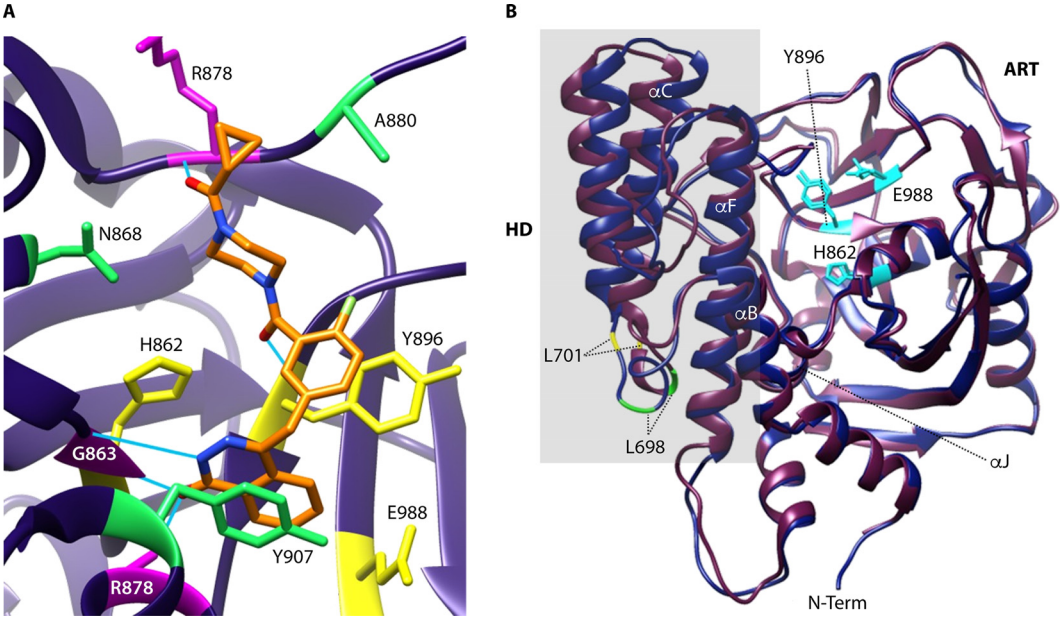

FIG 4 (A) Crystal structure of PARP1 bound to the inhibitor olaparib (orange) (PDB file 5ds3) (584). The catalytic triad, which is comprised of H862, Y896, and E988, is highlighted in yellow. Residues shown in hot pink are those to which hydrogen bonds (blue lines) form upon inhibitor binding to the protein (G863, R878, and S904). In addition, the inhibitor forms hydrogen bonds with Y896 of the catalytic triad (yellow). It is also predicted that the inhibitor participates in hydrophobic interactions with several other residues highlighted in green (A880, N868, and Y907) in addition to hydrophobic interactions predicted to occur at H862, G863, and R878. (B) Overlay of the crystal structures of the active conformation of the PARP1 enzyme from PDB file 4dqy (dark blue) and the inactive conformation of the enzyme from PDB file 1a26 (purple) (643, 644). Upon binding to DNA, the protein converts to the active conformation, resulting in unfolding, in the HD domain (shaded in gray). Residues comprising the catalytic triad (cyan) indicate the binding pocket of the protein. Residues L698 (green) and L701 (yellow) are also highlighted because their removal from the hydrophobic core of the HD domain has been predicted to play a role in the unfolding occurring in the HD upon activation.

to the DNA-bound form, crystal structures of the isolated PARP1 ART have shown an active site that is open and accessible for binding to inhibitors. The HD occludes access to the NAD^+-binding site (591), and the changes in the HD conformation allow increased access of substrates, leading to an increase in PARP1 activity (584). However, molecular dynamics (MD) calculations that have positioned an extended histone peptide tail into a rigid catalytic site have shown that the ART can accommodate a protein substrate in the absence of DNA (592). In addition to the structural changes that increase PARP1 activity, it is likely that the positioning of the region of automodification in close proximity to the catalytic domain will contribute to PARP1 DNA damage-dependent activity by increasing exposure to protein substrates. The positioning of the automodification region can also explain the strong preference for PARP1 to attach polymers to itself, rather than heteromodification of other molecules.

It is noteworthy that PARPs may also be activated by other factors, presumably corresponding to their diverse roles in cells. For example, PARP2 was shown to be activated by RNA (593). PARP1 could be activated by phosphorylation (594), by direct protein/protein interaction (595), and by ADP-ribosylation by PARP3 (45). An interaction with YB-1 was shown to control the level of PARylation depending on the significance of DNA damage (596). The full biological significance and molecular mechanisms of these alternate roles remain to be elucidated.

Research on the structure of PARP1, and other family members, has been focused mainly on the catalytic domains in order to explore new avenues for drug design. Studies have also been done to investigate the differences in the catalytic domains of PARP family members in efforts to understand the differences in the activities of polymerases versus mono(ADP-ribosyl)transferases. While recent studies have made great strides in unraveling the structure of PARP1 and in identifying its potential mechanism of action, there are significant gaps in understanding the process of

automodification, as well as the interaction between the DNA-binding and catalytic domains (42, 590, 591). Understanding these mechanisms is critical to gaining insight into critical cellular functions that include processes spanning the complete life cycle of the cell.

Inhibitor Classes

The pivotal role played by PARP in many biological processes makes it a prime target for inhibitory therapies. Nicotinamide (NAM) and 3-aminobenzamide (3-AB) were the first two inhibitors of PARP1 identified (597, 598). Benzamide and derivatives are effective inhibitors of PARPs owing to their structural similarity to NAD^+ (599). However, many early inhibitors were not specific to individual PARPs, had IC_{50} values in the micromolar range, and could sometimes have toxic side effects (600, 601). Many inhibitors that have progressed to clinical trials are effective in treating various forms of cancer. Yet the involvement of PARP1 in the progression of conditions such as chronic inflammation, diabetes, and neurological disorders has piqued the interest of researchers to explore other areas (602).

In 1992, Banasik and coworkers demonstrated that many inhibitors of both mono(ADP-ribosylation) and poly(ADP-ribosylation) exist and that the process may be regulated by a number of cellular metabolites and structural components. For example, metabolites such as unsaturated fatty acids and metabolites of tryptophan are strong and specific inhibitors of PARP1 *in vitro* (601). New inhibitor classes, such as isoquinolinones and quinazolinones, were discovered (601, 603). Tricyclic inhibitors, such as diazepinoindolones, are another class that has attracted the interest of researchers. These inhibitors were synthesized to maximize spatial and atomic interactions in the NAD^+-binding site of PARP1 (604). Isoquinolinones are another class of inhibitors that have been interesting to researchers, as they have been implicated in the protection from various diseases (601, 605). Since then, various studies identifying many of these inhibitors have been conducted (601). A detailed PARP1 pharmacophore has been developed (601, 603, 606–609).

Known PARP inhibitors include olaparib, rucaparib, niraparib, veliparib, simmiparib, talazoparib, and iniparib, with the first three being FDA approved (610–612). Olaparib is a bicyclic amide compound of the benzylphthalazinone class with an IC_{50} of 5 nM (613). This compound was shown to block tumor growth in a BRCA2-deficient xenograft mouse model and subsequently showed efficacy in several clinical trials against cancer (614). The catalytic site of the PARP1 ART domain with the binding mode of olaparib is shown in Fig. 4A. Olaparib forms hydrogen bonds with G863, R878, and S904 along with Y896 of the catalytic triad. In addition, hydrophobic interactions occur with A880, N868, Y907, H862, G863, and R878 (583). Veliparib and talazoparib are currently in clinical trials, while iniparib development has been discontinued (615–617).

The development of more specific PARP inhibitors is an area with rapid progress, and specific inhibitors for individual PARPs should help to elucidate their roles. It has become clear that inhibitors which mimic the binding of NAD^+ yield poor specificity for PARP1 (607, 618). In 2012, Wahlberg et al. showed that many well-characterized and high-affinity PARP inhibitors have promiscuous inhibitory activity, binding to several PARP family members (618). Hence, many recent studies focus on the identification of inhibitors which bind to the adenine subsite, located adjacent to the NAD^+-binding pocket (618). It is hypothesized that since the function of each family member is different, there should be some structural variations among PARPs. Since the ART is highly conserved, binding to an alternate site may elicit binding specificity (619). Haikaranen and coworkers identified an inhibitor, JW55, as well as several of its analogues which were shown to be potent and selective tankyrase inhibitors that bound to the adenine subsite (620). Continued development of inhibitors of the tankyrases target other binding sites, while some have been designed to target both the adenine subsite and the NAD^+-binding site, effectively tuning inhibitor specificity for the tankyrases (621).

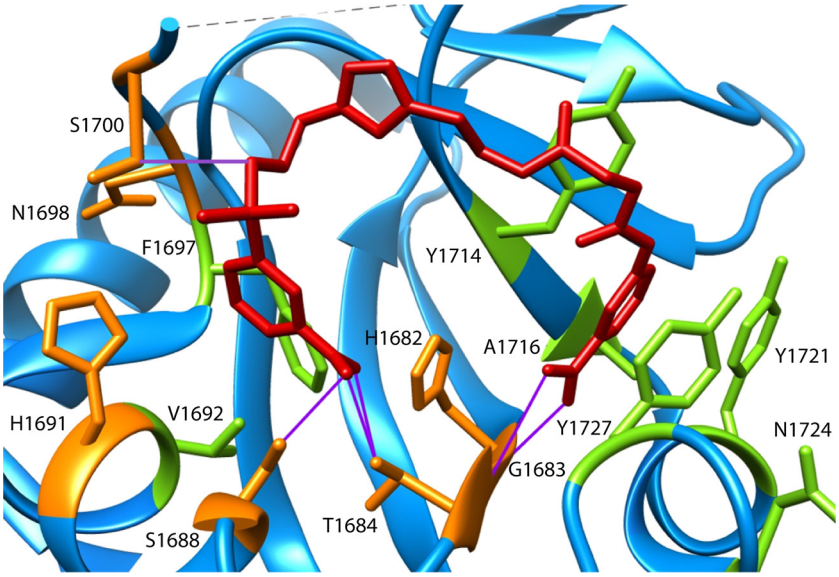

FIG 5 Close-up view of PARP14 bound to a bidentate inhibitor, H10 (red), which binds to both the NAD^+-binding pocket and adenine subsite to which its specificity can be attributed. The inhibitor participates in polar interactions (orange), hydrogen bonds (purple), and hydrophobic interactions (green) (619).

Bidentate inhibitors, which bind to both the NAD^+ and adenine subsites, have attracted much interest, as they may offer improved specificity (618). Analysis of crystal structures by Haikaranen et al. identified EB-47 as a bidentate inhibitor of PARP5a and -5b (622). Johannes et al. also have published work identifying bidentate inhibitors of the tankyrases (PARP5a and -5b) (623). The search for potential inhibitors of PARPs has led researchers to employ screening techniques that center on high-throughput methods. An example is work published by Peng and coworkers using a small-molecule microarray to screen for inhibitors of PARP14 (619). Using this method, another bidentate compound was identified. The compound, H10, containing a 3-sulfonamide benzoic acid moiety, inhibited PARP14 with an IC_{50} of 0.49 μM. The specificity of the inhibitor can be attributed to its ability to dually bind at both the NAD^+-binding pocket and the adenine subsite (619) (Fig. 5). Due to structural differences in the adenine subsite, this strategy can yield selectivity, and the inhibitor obtained in this case had 24-fold selectivity for PARP14 over PARP1. As described above, the PARP14 enzyme is associated with various inflammatory processes and several types of cancer (261, 624, 625).

Other screening methods used thermal shift analysis to observe increases in protein denaturation temperatures as an indication that a stabilizing binding interaction occurs between the protein and prospective inhibitor (618). Fluorescence-based assays have been developed for PARP1 and for the tankyrases (626). Inhibitors of the MARTs PARP15 and PARP10 were identified using an assay optimized for these enzymes (627). The IC_{50} values of the identified inhibitors agreed well with previous work using a different method. The establishment of this assay for screening PARP15 and PARP10 will allow for future studies toward the development of more potent and selective inhibitors. Recent work investigating the selectivity versus promiscuity of known inhibitors with the various PARP enzymes has also been conducted. The findings from this study provide data highlighting the structural basis of inhibitor binding (628).

Computational approaches have also been employed. Novel inhibitor scaffolds have been revealed by strategies including docking, active-site fingerprinting, and molecular dynamics (MD) simulations incorporating pharmacophore modeling to account for the dynamics of the potential inhibitors in the binding site (629–634). There are also new inhibitor therapies for use as single or combination therapy being developed by both

synthesis and modification of existing inhibitors (635). Recently a computational screening analysis identified a natural product known as ZINC67913374, which is predicted to be an improved inhibitor compared to olaparib (583). The combination of these theoretical, chemical, and biophysical approaches holds great promise for the development of selective inhibitors to target PARP functions within cells and tissues.

CONCLUSION

The review presented here gives an overview of recent findings in regard to the biological functions of the PARP family of proteins. Though the function of PARP1 is the best studied, this review highlights functions of many of the other family members which have been recently identified. Specifically, work was highlighted which implicated the function of this family of proteins in immune and inflammatory responses, suggesting that these enzymes are very promising for future therapeutic development. In addition, some of the most recent work pertaining to the structural and biophysical characteristics of PARP enzymes has offered solutions to the challenges of overcoming promiscuous inhibitor binding. The structural diversity and the wide array of biological functions in this class of enzymes attest to their importance in the progression of diseases in regard to both immune and inflammatory responses.

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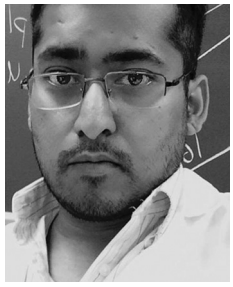

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